EXHIBIT R

Peak Inspiratory Flow Rate as a Criterion for Dry Powder Inhaler Use in Chronic Obstructive Pulmonary Disease

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Abstract

Dry powder bronchodilator devices have an internal resistance. Effective use depends on the patient generating an adequate inspiratory flow to break up the powder packets into particles less than 5-μm in diameter that can be inhaled into the lower respiratory tract. This disaggregation takes place inside the device before the dose leaves the inhaler; this process is increased if the acceleration is fast at the start of inhalation. Peak inspiratory flow depends on an individual's effort along with the strength of the respiratory muscles, which may be compromised in those with chronic obstructive pulmonary disease as a result of lung hyperinflation, hypoxemia, and muscle wasting. A handheld inspiratory flow meter can be used with an adjustable dial to simulate internal resistances of dry powder devices to assess whether a patient can achieve an optimal peak inspiratory flow rate of at least 60 L/min. Observational studies demonstrate that 19 to 78% of stable outpatients with chronic obstructive pulmonary disease and 32 to 47% of inpatients prior to discharge after admission for an exacerbation have a suboptimal peak inspiratory flow rate (<60 L/min). These data suggest that peak inspiratory flow rate should be measured against the simulated resistance of the specific dry powder bronchodilator device prior to prescription. If the peak inspiratory flow rate is less than 60 L/min, the patient may not achieve optimal clinical benefit, and a different delivery system, such as a metered-dose or soft mist inhaler or nebulized therapy, should be considered.

Keywords: drug delivery systems; bronchodilator effects; lung function tests

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Inhalation bronchodilators are the cornerstone of pharmacotherapy for patients with chronic obstructive pulmonary disease (COPD). Available bronchodilators include four short-acting and five long-acting inhaled β-agonists, two short-acting and four long-acting inhaled muscarinic antagonists, as well as two short-acting and five long-acting combinations of β-agonists and muscarinic antagonists (1). These medications are delivered by four different systems: pressurized metered-dose inhalers, soft mist inhalers, dry powder inhalers, and nebulizers. A pressurized metered-dose inhaler is actuated by pressing down on the canister, which releases an aerosol medication. Twisting the base of a soft mist inhaler compresses a spring, which then transfers a small volume of medication to the dosing chamber. Pressing the dose-release button propels a low-velocity aerosol plume. Dry powder inhalers are breath-actuated devices that require the individual to create turbulent inspiratory forces to disaggregate the powder into fine particles. The different types of nebulizers use a power source to generate an aerosol from liquid medications.

Pharmaceutical companies have developed dry powder delivery systems as a result of proprietary issues, technological innovations, and the phaseout of chlorofluorocarbon in inhalers (2). Dry powder devices approved by regulatory agencies for treatment of COPD include the Aerolizer (Novartis Pharma AG, Basel, Switzerland), Accuhaler/Diskus (GlaxoSmithKline, Research Triangle Park, NC), Breezhaler/Neohaler (Novartis Pharmaceuticals Corporation, East Hanover, NJ), Diskhaler (GlaxoSmithKline, Mississauga, ON, Canada), Ellipta (GlaxoSmithKline, Research Triangle Park, NC), Genuair/Pressair (AstraZeneca Pharmaceuticals LP, Wilmington, DE), HandiHaler (Boehringer Ingelheim International GmbH, Ingelheim Am Rhein, Germany), and Turbuhaler (AstraZeneca Pharmaceuticals LP, Wilmington, DE). Effective use of a dry powder inhaler depends on the patient generating an adequate inspiratory flow to disaggregate and disperse the powder into particles less than 5 μm in diameter that can be inhaled and deposited into the lower respiratory tract.

The 2017 Global Initiative for Chronic Obstructive Lung Disease strategy recommends "a personalization of initiating and escalating/de-escalating treatment" (1, p. 566). However, current strategies and recent guidelines on COPD offer no specific recommendations on which delivery system to use in which patient type to achieve optimal clinical outcomes (1, 3–6). The major objectives of the present Perspective are (*1*) to review characteristics of dry powder inhalers, (*2*) to describe the role of measuring peak inspiratory flow rate (PIFR) against the simulated resistance of a dry powder inhaler in assessment of the ability of patients with COPD to inhale the medication effectively, and (*3*) to report the prevalence of a suboptimal PIFR in stable outpatients with COPD as well as those hospitalized for an exacerbation. Finally, routine measurement of PIFR against the simulated resistance of the specific device is proposed before prescribing a dry powder bronchodilator to ensure that the patient has the inspiratory force to inhale the powder deep into the lower respiratory tract. This approach promotes the goal of personalizing inhalation bronchodilator therapy for patients with COPD.

Characteristics of Dry Powder Inhalers

Particles less than 5 μm in diameter have a high probability of being deposited in the lower respiratory tract. The absolute mass of drug particles this size with a single actuation is called the *fine-particle dose*. Each dry powder inhaler has a minimum threshold energy below which disaggregation is inefficient and results in a small fine-particle dose. Both *in vitro* and *in vivo* testing are performed to evaluate drug delivery from a dry powder inhaler.

In vitro assessments are conducted in accordance with regulatory guidance (7, 8). The internal resistance of an inhaler can be calculated using Ohm's law:

$$R = \frac{\sqrt{\Delta P}}{Q}$$

where R = resistance, ΔP = pressure drop across the inhaler for a set flow rate, and Q = flow rate in liters per minute (9). The resistance can be quantified by the inhalation flow required to produce a pressure drop of 4 kPa (10). This pressure drop value has been recommended for the *in vitro* characterization of the dose emitted from a dry powder inhaler (8). Various systems have been used by pharmaceutical companies for *in vitro* testing. The Andersen cascade impactor (11), a glass filter funnel (12), an electronic lung breathing simulator (13), and a next-generation impactor (14) have been used to assess dose delivery characteristics at inspiratory flow rates ranging from 30 to 100 L/min.

For *in vivo* evaluations, patients with COPD who have a range of airflow obstruction severities are tested. The percentages of patients able to generate a specific PIFR, usually 60 L/min or higher, through the dry powder inhaler are reported. Evaluations may also include patient comments and complaints about ease of using the device as well as preference for one device compared with another (12, 14).

Single-dose capsules and two types of multidose dry powder inhalers are available. Devices that contain bulk formulation in a reservoir are the most common. Another multidose type has premetered dispensed doses in packaged blisters inside the device. All drug powder particles are either attached to a carrier or are in the form of pellets. Dry powder inhalers are breath actuated, which requires the individual to create turbulent forces to disaggregate the powder into fine particles that can reach the lower respiratory tract (10).

In general, higher inspiratory flows are associated with improved performance of the dry powder devices and increase the dose of the medication inhaled by the patient (9, 15). A PIFR of at least 60 L/min through the device is considered optimal for the patient to break up the powder and inhale the fine particles into the lungs, whereas a PIFR less than 30 L/min is insufficient (16–19). Although Laube and colleagues (10, p. 1322) commented that the minimum PIFR "is probably 30 liters/minute," the clinical effectiveness of a PIFR between 30 and 60 L/min through the dry powder inhaler has been questioned (20, 21).

Each pharmaceutical company provides instructions in the prescribing information that describe how the patient should use the particular inhaler. With all dry powder inhalers, instructions state that, after preparing the device, the patient should breathe out completely while holding the inhaler away from the mouth and not exhale into the device. Table 1 lists the internal resistances and specific instructions for dry powder bronchodilators. Everard and colleagues (22) showed that disaggregation of particles takes place inside the device before the dose leaves the inhaler. It is increased if the acceleration is fast at the start of inhalation. Thus, patients should be instructed to inhale "forcefully from the beginning of inhalation" (10). Simple instructions for patients are to breathe in "hard and fast" (23).

Peak Inspiratory Flow Rate

The ability of an individual to generate peak inspiratory flow depends on the level of effort and the strength of the respiratory muscles. PIFR is obtained routinely as part of the flow–volume loop. However, there is minimal resistance to airflow in most pulmonary function testing systems, whereas all dry powder inhalers have an internal resistance. In clinical studies, PIFR has generally been measured after a complete exhalation to simulate instructions for using a dry powder inhaler (Table 1). Magnussen and colleagues (24) showed that inhalation instructions can affect the results of PIFR. The PIFR measured through the HandiHaler device was approximately 13 L/min higher when subjects performed a "fast, forceful" inhalation compared with using a "slow, deep" technique (24).

Investigators have frequently used the In-Check DIAL (Clement Clerke International Ltd., Harlow, UK) to measure PIFR because the instrument is portable, has a one-way mouthpiece with a valve, and provides an adjustable dial with different-sized openings to simulate device resistances. With the original In-Check DIAL, internal resistances can be simulated for a metered-dose inhaler, Diskus, or Turbuhaler, along with Aereolizer and HandiHaler devices using specific adapters. In 2016, the In-Check DIAL was updated to allow measurement of additional dry powder inhalers. The new In-Check DIAL (G16) includes five resistance groups for dry powder inhalers classified as low (one device), medium low (three devices), medium (three devices), medium high (three devices), and high (two devices) (25).

The In-Check DIAL measures inspiratory flow from 15 to 120 L/min. Manufacturing specifications indicate that PIFR against a resistance is accurate to ±10% or 10 L/min, whichever is greater (25). The test–retest reliability of PIFR measured with the Diskus device was satisfactory (72.8 ± 18.4 vs. 74.9 ± 17.9 L/min; $P = 0.59$) in 45 stable patients with COPD (26).

Table 1. Internal resistances and prescribing information for dry powder inhalers

Dry Powder Inhaler (Bronchodilator)	Internal Resistance* ($kPa^{0.5}$ [L/min]) (Reference)	Prescribing Information for Inhaling
Aerolizer (formoterol)	0.019 (18)	Breathe in quickly and deeply.
Diskhaler (salmeterol)	0.021 (35)	Inhale as quickly and deeply as you can.
Breezhaler/Neohaler (indacaterol and/or glycopyrrolate)	0.022 (12)	Breathe in rapidly and steadily, as deeply as you can.
Accuhaler/Diskus† (salmeterol)	0.027 (18, 36)	Breathe in quickly and deeply.
Ellipta† (vilanterol and/or umeclidinium)	0.029 (13, 27)	Take 1 long, steady, deep breath in.
Genuair/PressAir (aclidinium)	0.031 (37)	Breathe in quickly and deeply.
Turbuhaler† (formoterol/budesonide‡)	0.036 (38)	Inhale deeply and forcefully.
HandiHaler (tiotropium)	0.051 (14, 17)	Breathe in deeply until your lungs are full. To get your full daily dose, you must again, breathe out completely and for a second time, breathe in.

*Values are rounded to one-thousandths.
†Contains or may contain an inhaled corticosteroid.
‡Budesonide is a corticosteroid.

Prevalence of a Suboptimal Peak Inspiratory Flow Rate in Patients with COPD

A limited number of investigations have measured PIFR in stable outpatients with COPD as well as in those admitted to the hospital with an exacerbation. In a majority of these studies, the simulated resistance of the Diskus has been used with the In-Check DIAL because this device has a medium resistance (10). Comparative studies show that the higher the internal resistance of the dry powder inhaler, the lower the PIFR achieved (14, 16, 18, 20, 24). Prime and colleagues (27) showed that there is a linear trend for PIFR to decrease as disease severity increases in patients with COPD ($P < 0.001$).

Stable Outpatients with COPD

Janssens and colleagues (18) studied 26 patients with COPD who were 70 years of age or older with a mean FEV_1 of 49% predicted. PIFR measured with the In-Check DIAL set at zero resistance was significantly correlated ($P < 0.005$ for all variables) with age ($r = -0.50$), maximal inspiratory pressure ($r = 0.42$), and maximal expiratory pressure ($r = 0.50$), but not with percent predicted values for FEV_1 and FVC (18). PIFR was less than 60 L/min in 36% tested against the Diskus device and in 78% tested with the Turbuhaler device (18). Mahler and associates (26) recruited patients in the clinic who were at least 60 years of age and had a FEV_1 less than or equal to 50% predicted. Of 213 patients, 19% exhibited a PIFR less than 60 L/min against the resistance of the Diskus (26). The clinical phenotype of patients with a suboptimal PIFR included a predominance of female sex (80% vs. 48%; $P < 0.001$), as well as shorter height ($P < 0.001$) and lower values for FVC ($P < 0.001$) and inspiratory capacity (IC) ($P < 0.014$) percent predicted than those who had PIFR greater than or equal to 60 L/min (26).

Patients Hospitalized with COPD Exacerbation

Sharma and colleagues (28) measured PIFR on the day prior to discharge in 268 patients admitted to the hospital for a COPD exacerbation. The study was performed at seven hospitals (number of beds ranged from 80 to 1,300) in the United States and included three academic centers, three community hospitals, and one federal hospital (28). Eighty-five patients (32%) exhibited a PIFR less than 60 L/min against the simulated resistance of the Diskus (28). Patients with PIFR less than 60 L/min ($n = 85$) were older (66.2 ± 10.0 vs. 62.1 ± 9.4 yr; $P = 0.006$), more likely to be female (61% vs. 42%; $P = 0.014$), and more likely to have a history of ischemic heart disease ($P = 0.015$) and pneumonia ($P = 0.029$) than those who had PIFR greater than or equal to 60 L/min ($n = 85$) (28).

In a study performed at an academic medical center, Loh and colleagues (29) found that 47% of 179 patients hospitalized for a COPD exacerbation had a PIFR less than 60 L/min prior to discharge. Of note, PIFR was measured at FRC, and the In-Check DIAL was set at no resistance (29). Readmissions after discharge were assessed by chart review. The investigators found significant differences in number of days for the next all-cause readmission based on PIFR less than 60 L/min (39.7 ± 10.0 d) and greater than 60 L/min (73.4 ± 9.6 d) ($P = 0.02$), as well as in number of days to next COPD readmission (64.0 ± 20.8 vs. 147.0 ± 17.2 d; $P = 0.0035$) (29).

Discussion

To provide optimal bronchodilator therapy, the health care professional should assess individual patient characteristics, including physical and cognitive function, the severity and frequency of symptoms, exacerbation history and future risks, and any comorbidities (1). Ideally, the patient should be queried about previous experience with different inhalation bronchodilators and any preference for the type of delivery system. Medication cost is another important consideration. Health insurance policies may have contracts with pharmaceutical companies that can determine which particular medication is approved or covered for an individual patient.

In prescribing an inhalation bronchodilator for a patient with COPD, the health care provider has three decisions to make: short-acting versus long-acting, β-agonist versus muscarinic antagonist or a fixed-dose combination of the two classes, and the particular delivery system. Currently, strategies and guidelines do not

provide specific recommendations on which bronchodilator medication and which delivery system should be prescribed for an individual patient. Although health care professionals use their best judgment to make these decisions, the preliminary results of a survey of pulmonologists revealed that only 54% reported that they "were very knowledgeable about the devices used in treatment of COPD" (30, p. A7816). Observational studies demonstrate that 19 to 78% of outpatients with COPD and 32 to 47% of inpatients prior to discharge after admission for an exacerbation have a suboptimal PIFR (18, 26, 28, 29).

Only limited data are available regarding whether someone with a suboptimal PIFR will achieve clinical benefit with a dry powder bronchodilator. Borgström and colleagues (31) found that drug deposition using radiolabeled budesonide in the Turbuhaler device was reduced from 28 to 15% when PIFR was reduced from 58 L/min to 36 L/min in 10 healthy subjects. Mahler and colleagues (32) compared changes in lung function in 20 patients with COPD after the patients inhaled a single dose of a nebulized and a dry powder long-acting β-agonist. All subjects had a PIFR less than 60 L/min against the resistance of the Diskus on two different test dates (32). In this single-blind, open-label study, there were significantly greater increases in FVC (+14% vs. + 8%; $P = 0.02$) and IC (+13% vs. + 8%; $P = 0.05$), but not in FEV_1 (+11% vs. +7%; $P = 0.17$), at 2 hours (peak effect) after a single dose of a nebulized arformoterol compared with a single dose of dry powder salmeterol in the Diskus (32). These findings demonstrate greater volume responses with a nebulized than with a dry powder β-agonist bronchodilator in those with a suboptimal PIFR (32).

Effort and technique as well as adequate respiratory muscle strength are important factors for an individual's ability to generate the highest peak inspiratory flow. How can patients with a suboptimal PIFR be identified? Using multiple regression analysis, Mahler and colleagues (26) found that age, sex, height, FVC percent predicted, and IC percent predicted were independent predictors of PIFR against the simulated resistance of the Diskus in 213 patients with COPD ($R^2 = 36\%$). Janssens and colleagues (18) demonstrated a significant correlation between PIFR and both inspiratory and expiratory mouth pressures. Two factors—female sex and hyperinflation of the lungs—may contribute to reduced inspiratory muscle strength. Females have lower values for lung function, including inspiratory mouth pressures, than males (33). In two different cohorts of patients with COPD, there were significantly more females in subgroups with a PIFR less than 60 L/min than in subgroups with a PIFR greater than or equal to 60 L/min (26, 28). In addition, lung hyperinflation can affect PIFR by two mechanisms. The vertical muscle fibers of the diaphragm are shortened, which reduces strength, and there is an added elastic load that must be overcome during inspiration (34). In one study, IC percent predicted, a noninvasive estimate of hyperinflation, was significantly lower in those with a PIFR less than 60 L/min than in those with a PIFR greater than or equal to 60 L/min against the resistance of the Diskus (26). Respiratory muscle strength may also be compromised because of hypoxemia and muscle wasting, both of which are common in patients with advanced COPD.

Although patient characteristics should be considered, a direct approach is to measure PIFR against the simulated resistance of the dry powder bronchodilator inhaler being considered for prescription. Instructions and demonstration of correct technique are essential for patients to achieve their highest PIFR. In many institutions, a respiratory therapist or pulmonary function technician is responsible for obtaining the PIFR measurements. On the basis of knowledge of dry powder inhalational therapy along with the observed prevalence of suboptimal PIFR in patients with COPD, I propose the following paradigm:

1. PIFR should be routinely measured in patients with COPD in the outpatient clinic and prior to discharging a patient from the hospital following an exacerbation if prescribing a dry powder bronchodilator is being considered.
2. A PIFR of 60 L/min or higher is reassuring. The patient should be able to successfully inhale the dry powder bronchodilator medication as long as he or she performs an appropriate inhalation technique.
3. A PIFR less than 60 L/min is concerning. The health care professional should then consider an alternative bronchodilator delivery system, such as a pressurized metered-dose inhaler, a soft mist inhaler, or nebulized therapy.
4. It is reasonable to recheck PIFR if the patient's clinical status has changed. One particular situation is after the patient has recovered from an exacerbation if the health care professional intends to prescribe a dry powder bronchodilator.

Finally, prospective testing is needed to examine lung function, patient-reported outcomes, and hospital readmissions in patients with COPD, comparing a dry powder bronchodilator against an alternative delivery system based on a PIFR threshold.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, *et al.* Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med* 2017;195:557–582.

2 Hendeles L, Colice GL, Meyer RJ. Withdrawal of albuterol inhalers containing chlorofluorocarbon propellants. *N Engl J Med* 2007;356: 1344–1351.

3 COPD Foundation. COPD Foundation pocket consultant guide [accessed 2017 Feb 10]. Available from: https://www.copdfoundation.org/Praxis/Community/Blog/Article/747/Resource-of-the-Month-Just-updated-The-COPD-Foundation-s-Pocket-Consultant-Guide.aspx

4 Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, Trigueros JA, Piñera P, Simón A, Riesco JA, *et al.* A new approach to grading and treating COPD based on clinical phenotypes: summary of the Spanish COPD guidelines (GesEPOC). *Prim Care Respir J* 2013;22:117–121.

5 Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, Marciniuk DD, Denberg T, Schünemann H, Wedzicha W, *et al.*; American College of Physicians; American College of Chest Physicians; American Thoracic Society; European Respiratory Society. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011;155:179–191.

6 Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946.

7 U.S. Food and Drug Administration (FDA). Guidance for industry: metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products: chemistry, manufacturing, and controls documentation. Rockville, MD: U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER); 1998.

8 European Pharmacopeia. Preparations for inhalation: aerodynamic assessment of fine particles. Strasbourg, France: European Pharmacopeia Commission; 2001;2.9.18.

9 Clark AR, Hollingworth AM. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers—implications for *in vitro* testing. *J Aerosol Med* 1993;6:99–110.

10 Laube BL, Janssens HM, de Jongh FHC, Devadason SG, Dhand R, Diot P, Everard ML, Horvath I, Navalesi P, Voshaar T, *et al*.; European Respiratory Society; International Society for Aerosols in Medicine. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011;37:1308–1331.

11 Chodosh S, Flanders JS, Kesten S, Serby CW, Hochrainer D, Witek TJ Jr. Effective delivery of particles with the HandiHaler dry powder inhalation system over a range of chronic obstructive pulmonary disease severity. *J Aerosol Med* 2001;14:309–315.

12 Pavkov R, Mueller S, Fiebich K, Singh D, Stowasser F, Pignatelli G, Walter B, Ziegler D, Dalvi M, Dederichs J, *et al*. Characteristics of a capsule based dry powder inhaler for the delivery of indacaterol. *Curr Med Res Opin* 2010;26:2527–2533.

13 Grant AC, Walker R, Hamilton M, Garrill K. The ELLIPTA dry powder inhaler: design, functionality, *in vitro* dosing performance and critical task compliance by patients and caregivers. *J Aerosol Med Pulm Drug Deliv* 2015;28:474–485.

14 Chapman KR, Fogarty CM, Peckitt C, Lassen C, Jadayel D, Dederichs J, Dalvi M, Kramer B. Delivery characteristics and patients' handling of two single-dose dry-powder inhalers used in COPD. *Int J Chron Obstruct Pulmon Dis* 2011;6:353–363.

15 Ganderton D. General factors influencing drug delivery to the lung. *Respir Med* 1997;91:13–16.

16 Atkins PJ. Dry powder inhalers: an overview. *Respir Care* 2005;50: 1304–1312.

17 Al-Showair RAM, Tarsin WY, Assi KH, Pearson SB, Chrystyn H. Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? *Respir Med* 2007;101:2395–2401.

18 Janssens W, VandenBrande P, Hardeman E, De Langhe E, Philps T, Troosters T, Decramer M. Inspiratory flow rates at different levels of resistance in elderly COPD patients. *Eur Respir J* 2008;31:78–83.

19 Payne N, Beard S, Brucklebank D, Ram F, Wright J, Taylor R. Clinical and cost-effectiveness of inhaler devices for children with chronic asthma. Report commissioned by NHS R&D HTA Programme on behalf of the National Institute of Clinical Excellence, August 2000.

20 Broeders MEAC, Molema J, Vermue NA, Folgering HTM. In Check Dial: accuracy for Diskus and Turbuhaler. *Int J Pharm* 2003;252:275–280.

21 Chrystyn H. Is inhalation rate important for a dry powder inhaler? Using the In-Check Dial to identify these rates. *Respir Med* 2003;97:181–187.

22 Everard ML, Devadason SG, Le Souëf PN. Flow early in the inspiratory manoeuvre affects the aerosol particle size distribution from a Turbuhaler. *Respir Med* 1997;91:624–628.

23 Mahler DA. COPD: answers to your questions. Minneapolis, MN: Two Harbors Press; 2015. p. 56.

24 Magnussen H, Watz H, Zimmermann I, Macht S, Greguletz R, Falques M, Jarreta D, Garcia Gil E. Peak inspiratory flow through the Genuair inhaler in patients with moderate or severe COPD. *Respir Med* 2009; 103:1832–1837.

25 Alliance Tech Medical. Updating In-Check DIAL 2016 [accessed 2017 Feb 10]. Granbury, TX: Author. Available from: http://alliancetechmedical.com/index.php/download_file/view/147/141/

26 Mahler DA, Waterman LA, Gifford AH. Prevalence and COPD phenotype for a suboptimal peak inspiratory flow rate against the simulated resistance of the Diskus dry powder inhaler. *J Aerosol Med Pulm Drug Deliv* 2013;26:174–179.

27 Prime D, de Backer W, Hamilton M, Cahn A, Preece A, Kelleher D, Baines A, Moore A, Brealey N, Moynihan J. Effect of disease severity in asthma and chronic obstructive pulmonary disease on inhaler-specific inhalation profiles through the ELLIPTA dry powder inhaler. *J Aerosol Med Pulm Drug Deliv* 2015;28:486–497.

28 Sharma GG, Mahler DA, Mayorga V, Deering K, Ganapathy V. Prevalence of low peak inspiratory flow rate (PIFR) in chronic obstructive pulmonary disease (COPD) patients at discharge after an exacerbation - interim findings from a prospective study [abstract]. *Am J Respir Crit Care Med* 2016;193:A1506.

29 Loh CH, Lovings TM, Ohar JA. Low inspiratory flow rates predict COPD and all cause readmissions [abstract]. *Am J Respir Crit Care Med* 2016;193:A1125.

30 Braman SS, Carlin BW, Dhand R, Hanania NA, Mahler DA, Ohar JA, Pinto-Plata V, Shah T, Turenne M, Eubanks D. Results of a pulmonologist survey regarding attitudes and practices with inhalational devices for COPD [abstract]. *Am J Respir Crit Care Med* 2016;193:A7816.

31 Borgström L, Bondesson E, Morén F, Trofast E, Newman SP. Lung deposition of budesonide inhaled via Turbuhaler: a comparison with terbutaline sulphate in normal subjects. *Eur Respir J* 1994;7: 69–73.

32 Mahler DA, Waterman LA, Ward J, Gifford AH. Comparison of dry powder versus nebulized β-agonist in patients with COPD who have suboptimal peak inspiratory flow rate. *J Aerosol Med Pulm Drug Deliv* 2014;27:103–109.

33 Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE; Cardiovascular Health Study Research Group. Respiratory muscle strength in the elderly: correlates and reference values. *Am J Respir Crit Care Med* 1994;149:430–438.

34 O'Donnell DE, Banzett RB, Carrieri-Kohlman V, Casaburi R, Davenport PW, Gandevia SC, Gelb AF, Mahler DA, Webb KA. Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. *Proc Am Thorac Soc* 2007;4:145–168.

35 Srichana T, Martin GP, Marriott C. Dry powder inhalers: the influence of device resistance and powder formulation on drug and lactose deposition in vitro. *Eur J Pharm Sci* 1998;7:73–80.

36 Broeders MEAC, Molema J, Folgering HTM. Resistivities of placebo and active Diskus inhalers compared. *Int J Pharm* 2001;228: 219–222.

37 Chrystyn H, Niederlaender C. The Genuair inhaler: a novel, multidose dry powder inhaler. *Int J Clin Pract* 2012;66:309–317.

38 Azouz W, Chetcuti P, Hosker H, Saralaya D, Chrystyn H. Inhalation characteristics of asthma patients, COPD patients and healthy volunteers with the Spiromax and Turbuhaler devices: a randomised, cross-over study. *BMC Pulm Med* 2015;15:47.

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Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate

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Abstract

Background: A peak inspiratory flow rate (PIFR) of <60 L/min against the internal resistance (resist) of a dry powder inhaler (DPI) may limit the ability of a patient with chronic obstructive pulmonary disease (COPD) to achieve bronchodilation. The hypothesis was that lung function would be higher with a beta-agonist inhaled via nebulization compared with dry powder in patients with COPD who exhibit a PIFRresist of <60 L/min against the Diskus®.

Methods: This study was randomized, single-blind, and crossover with spirometry and inspiratory capacity (IC) measured at 15, 30, and 120 min post treatment. The efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer was compared with salmeterol dry powder (50 μg) via Diskus. The primary outcome was the change in lung function from baseline at 2 hr as these two inhaled beta-agonists have the similar peak bronchodilator effect as measured by forced expiratory volume in 1 sec (FEV1).

Results: Twenty patients (15 females/5 males) with postalbuterol FEV1 of 0.83 ± 0.31 L (38 ± 12% predicted) and PIFRresist of 53 ± 5 L/min completed the study. At 15 min, improvements in FEV1, forced vital capacity (FVC), and IC were significantly higher with arformoterol than with salmeterol. At 2 hr, changes in FVC and IC, but not FEV1, were significantly higher with arformoterol. At visit 3, patient preference was similar for salmeterol Diskus (n=8) and arformoterol solution (n=7), whereas five patients reported no preference.

Conclusions: At peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in patients with COPD who had a PIFRresist of <60 L/min. Bronchodilator therapy via nebulization should be considered in patients with COPD who have a suboptimal PIFRresist against a particular DPI.

Key words: peak inspiratory flow rate, dry powder inhaler, nebulized bronchodilator, lung function

Introduction

AN INITIAL FAST INHALATION is recommended with a dry powder inhaler (DPI) to generate a turbulent force in order to deaggregate the powder pellets into particles of <5 μm that can be deposited into the lower respiratory tract.[1] Peak inspiratory flow rate (PIFR) has been used to assess the ability of a patient to inhale a dry powder bronchodilator. A PIFR of ≥60 L/min against the internal resistance (resist) of the particular DPI is considered optimal to inhale the dry powder bronchodilator.[2,3] Increased patient age, a lower level of education, inadequate instructions by health-care providers, and a low PIFR are reasons why some patients with chronic obstructive pulmonary disease (COPD) do not achieve clinical benefit using a DPI.[4,5] Recently, Mahler and colleagues[6] demonstrated that 19% of 213 patients with advanced COPD [age ≥60 years and forced expiratory volume in 1 sec (FEV1) ≤50% predicted] had a PIFRresist of <60 L/min against the simulated resistance of the Diskus® DPI.

Alternative approaches to using a DPI for bronchodilation are inhaling an aerosol solution from a nebulizer and using a metered-dose inhaler (MDI) with a spacer.[1] In randomized controlled trials, patients with moderate to severe COPD show similar improvements in FEV1 at 2 hr with a long-acting beta-agonist delivered by MDI (salmeterol) or DPI (formoterol) and by nebulization (arformoterol/formoterol).[7–16]

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Although PIFRresist was not measured in these study patients, their baseline characteristics do not fit the clinical phenotype—female gender, shorter stature, and reduced values for forced vital capacity (FVC) and inspiratory capacity (IC) as percent predicted—of patients with COPD who exhibit a suboptimal PIFRresist (<60 L/min) against the simulated resistance of the Diskus.[6]

The objective of this study was to compare the acute changes in lung function with the recommended initial fast and hard inhalation of a beta-agonist bronchodilator from a DPI (salmeterol Diskus) with the tidal breathing of aerosol solution delivered via nebulization (arformoterol) in patients with COPD who have a PIFRresist of <60 L/min against the Diskus. The rationale for such investigation is that patients with a suboptimal PIFRresist may be "at risk" for not being able to completely inhale a dry powder bronchodilator into the lower respiratory tract.[3,11] Salmeterol dry powder was selected for comparison because: (1) it is a widely used beta-agonist in the Diskus; (2) the Diskus has a lower internal resistance than formoterol Turbuhaler®[2,3,11,12]; and (3) patients with moderate-severe COPD and presumed optimal PIFRresist (>60 L/min) show similar peak FEV1 responses at 2 hr after inhaling salmeterol via MDI and arformoterol via nebulizer.[9,10] The hypothesis of our study is that lung function measured at 2 hr post dose would be greater with a beta-agonist bronchodilator delivered by nebulization than with inhalation from a DPI in patients with COPD who exhibit a PIFRresist of <60 L/min.

Materials and Methods

Study subjects

Inclusion criteria were: diagnosis of COPD[13]; at least 10 pack-year history of cigarette smoking; age ≥60 years; current or previous use of the Diskus DPI (salmeterol or salmeterol/fluticasone); and PIFR of <60 L/min using the In-check DIAL® against the simulated resistance of the Diskus. Exclusion criteria were: inability to understand verbal instructions; any concomitant disease that might interfere with study procedures; unstable clinical disease; and inability to withhold short- and long-acting bronchodilators on the days of testing. Eligible patients were recruited after they completed pulmonary function tests at our institution.

Study design

This randomized, open-label, single-blind, crossover study was performed between July 2011 and October 2012. The protocol was approved by the Committee for the Protection of Human Subjects at Dartmouth College (#22812). The study was registered with ClinicalTrials.gov: NCT01391559. All patients signed the appropriate consent form. Patients participated in three visits, each 2–3 days apart. Testing procedures at these visits are described in Table 1. At visit 2, patients were randomized to the study medication. The pulmonary function technician who collected patient data at visits 2 and 3 was blinded to the study medication. All patients held short-acting bronchodilators for 4 hr and long-acting bronchodilators for 12 hr (if used twice daily) and 24 hr (if used once daily) prior to visits 2 and 3.

Methods

The In-Check DIAL (Clement Clarke International Ltd., Harlow, UK) was used to measure PIFR against the simulated internal resistance of the Diskus. According to the manufacturer, the In-Check DIAL is accurate within ±10% or ±10 L/min, whichever is greater. The test–retest reliability of PIFRresist was excellent in 45 patients with advanced COPD.[6] At visit 1, spirometry, IC, and diffusing capacity (NSpire HD3000; Nspire Health Inc., Longmont, CO) were measured using standard techniques.[14,15] Values were expressed as percentages of predicted values.[16,17] At visits 2 and 3, patients performed spirometry and IC maneuvers at baseline and 15, 30, and 120 min after completing inhalation of 50 μg of salmeterol from the Diskus or 15 μg of arformoterol solution administered by the UP-MIST nebulizer (Hospitak REF 3952-E; Birkerod, Denmark) using compressed gas.

Analysis

The primary outcome was the change in lung function (FEV1, FVC, and IC) at 2 hr after inhalation of the study medication compared with baseline. The secondary outcome was patient preference for salmeterol Diskus or arformoterol solution via nebulizer. Paired *t* tests were used to compare these outcomes at equivalent time periods. Results are presented as means ± standard deviation (SD) values. A $p \leq 0.05$ was considered significant.

Results

Enrollment, allocation, follow-up, and analysis of patients are shown in Figure 1. Descriptive characteristics of the 15 female and five male patients with COPD are shown in Table 2. All patients had a PIFRresist of <60 L/min at visit 1 (53 ± 5 L/min). The duration of COPD diagnosis was 8.7 ± 4.3 years, and smoking history was 50.8 ± 22.0 pack-years. For patients currently using the Diskus DPI, four reported that the medication improved their breathing difficulty, whereas five were unsure. For patients who previously used the Diskus, one patient reported that the medication improved her breathing difficulty, five reported no benefit, and five patients were unsure.

There were no significant differences in lung function at baseline between visits 2 and 3. Baseline FEV1 at visit 2 was 0.72 ± 0.30 L (33 ± 11% predicted) and at visit 3 was 0.71 ± 0.29 L (33 ± 11% predicted) ($p = 0.37$). Changes in lung function from baseline with the study medications are displayed in Table 3. At 15 min, improvements in all three measures of lung function were significantly greater with arformoterol compared with salmeterol. At 2 hr, the changes in FVC and IC, but not FEV1, were significantly higher with arformoterol (Table 3 and Figs. 2–4). Eight patients preferred salmeterol Diskus, seven patients preferred arformoterol solution, and five patients had no preference.

Discussion

The major findings of this study of 20 patients with COPD who had a suboptimal PIFRresist against the Diskus were: (1) for peak bronchodilator effect at 2 hr, the increases in FVC and IC, but not FEV1, were greater for arformoterol compared

TABLE 1. PROCEDURES

Visit 1

1. Patient signed informed consent form.
   The patient completed the self-administered computerized baseline dyspnea index.[30]
2. Patient read the following questions, and circled the appropriate answer:
   a. If you are using the Diskus® device (Serevent® or Advair®) at the present time, does the medication improve your breathing difficulty? Yes or No or Not Sure
   b. If you are not using the Diskus® device (Serevent® or Advair®) at the present time, but did take it previously, did the medication improve your breathing difficulty? Yes or No or Not Sure
3. Patient performed spirometry and inspiratory capacity (IC) maneuvers before and 30 min after inhaling two puffs (180 μg) of albuterol via metered-dose inhaler followed by measurement of single-breath diffusing capacity.
4. Each patient was familiarized with the inhalational technique for salmeterol Diskus and for nebulized arformoterol per instructions in the respective package inserts. The order of familiarization was randomized and consisted of the following written instructions (taken from the package insert) and then demonstrated by a respiratory therapist (LAW).

   Salmeterol Diskus
   a. Hold the Diskus in one hand and put the thumb of your other hand on the thumbgrip. Push the thumb away from you as far as it will go until the mouthpiece appears and snaps into position.
   b. Hold the Diskus in a level, flat position with the mouthpiece toward you. Slide the lever away from you as far as it will go until it clicks. The Diskus is now ready to use.
   c. Before inhaling your dose from the Diskus, breathe out (exhale) fully while holding the Diskus level and away from your mouth. Remember, never breathe out into the Diskus device. Put the mouthpiece to your lips. Breathe in quickly and deeply through the Diskus. Do not breathe in through your nose.
   d. Remove the Diskus from your mouth. Hold your breath for about 10 sec, or for as long as is comfortable. Breathe out slowly.

   Arformoterol solution via nebulizer
   a. Sit in a comfortable upright position. Place the mouthpiece in your mouth.
   b. Breathe as calmly and evenly as possible until no more mist is formed in the nebulizer. It takes about 5 to 10 min for the treatment.

Visit 2 (2–3 days after Visit 1)

1. Patients arrived in the pulmonary function laboratory between 11 AM and 12 noon. After a 10-min rest, patients performed spirometry and IC maneuvers. Patients were then randomized to open-label salmeterol 50 μg via Diskus or arformoterol solution 15 μg/2 mL via UP-MIST nebulizer (Hospitak REF 3952-E; Birkerod, Denmark) using compressed gas. Nebulization was completed in 7–8 min. The technician performing the pulmonary function testing was blinded to the assigned medication.
2. At 15, 30, and 120 min after inhaling the medication, the patient performed spirometry and IC maneuvers.

Visit 3 (2–3 days after Visit 2)

1. The same procedures were used as described for visit 2 except the alternative medication was administered. At the end of visit 3, the patient was asked: "Which medication do you prefer—salmeterol Diskus or arformoterol solution in nebulizer—for helping your breathing difficulty? Circle one of the two medications."

with salmeterol; and (2) patient preference was similar for arformoterol and salmeterol.

It is important to consider baseline characteristics of our patients in interpreting the results. As an inclusion criterion, all patients had a PIFR of <60 L/min against the simulated resistance of the Diskus. Patients were predominantly female (75%), had a low diffusing capacity (47 ± 16% predicted), and reported substantial breathlessness with activities of daily living (self-administered computerized baseline dyspnea index = 4.7 ± 1.6). The predominance of females in our study was likely a result of women having lower absolute values for lung function compared with men, and the requirement of a threshold value for PIFRresist. Nineteen of the 20 patients in our study had a diffusing capacity below the lower limit of normal, consistent with the emphysema phenotype of COPD.

Standard and approved doses of salmeterol Diskus (50 μg) and arformoterol solution (15 μg) were evaluated in this study. We considered that these doses were appropriate for comparison based on results of two previous randomized controlled trials in which salmeterol via MDI (42 μg) and arformoterol solution (15 μg) demonstrated similar peak bronchodilator effect for FEV1.[9,10] Neither FVC nor IC results were reported in these trials.[9,10] Furthermore, the dose of salmeterol delivered by MDI (42 μg), which was discontinued in December 2007 because of its chlorofluorocarbon propellant, is equivalent to the dose delivered by Diskus (50 μg).

The responses in lung function were highly variable among individuals as shown in Figures 2–4. The significantly greater improvements in lung function at 15 min with arformoterol are consistent with a more rapid onset of action than with salmeterol.[9] Although the mean differences in FEV1 between arformoterol and salmeterol were similar at 15 min (33 mL) and 2 hr (32 mL), statistical comparison showed no difference for FEV1 at 2 hr between medications. This may be due in part to response variability as evident by the high SD with salmeterol therapy at 2 hr. In contrast, the increases in FVC and IC at 2 hr were significantly greater with arformoterol than with salmeterol. These results support the hypothesis of the study, and are consistent with previous studies that demonstrate bronchodilator responsiveness is

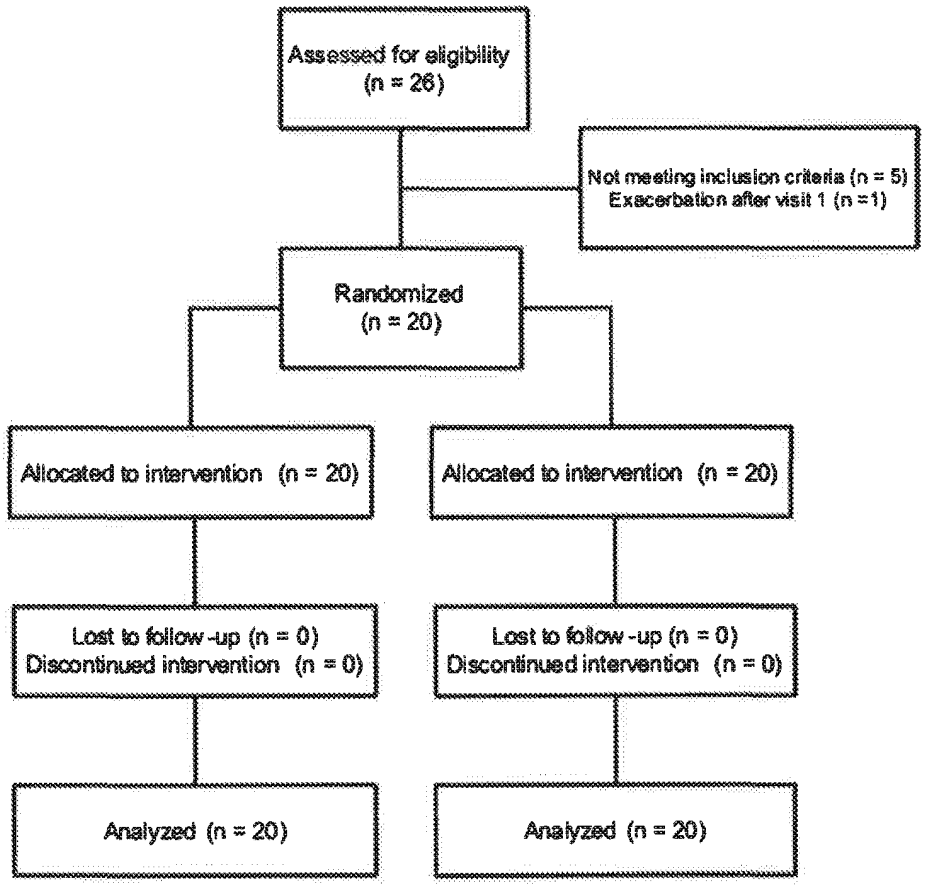

FIG. 1. Enrollment, allocation, follow-up, and analysis of patients. The figure shows that 20 patients completed testing with each arm of treatment (arformoterol and salmeterol). Based on randomization, 10 patients received arformoterol first, and 10 patients received salmeterol first. Subjects then crossed over to the other therapy.

TABLE 2. DESCRIPTIVE CHARACTERISTICS OF THE 20 PATIENTS

Variable	*Values*	*% predicted*
Age (yr)	71.6 ± 7.4	
Gender (female/male)	15/5	
Height (cm)	159.8 ± 9.5	
Weight (kg)	78.7 ± 20.8	
PIFRresist (L/min)	53.3 ± 5.0	
FEV1 (L)	0.76 ± 0.27	35 ± 11
post-BD FEV1 (L)	0.83 ± 0.31	38 ± 12
FVC (L)	1.98 ± 0.66	68 ± 19
post-BD FVC (L)	2.15 ± 0.65	74 ± 19
post-BD FEV_1/FVC (%)	38.8 ± 8.1	
IC (L)	1.48 ± 0.40	70 ± 13
post-BD IC (L)	1.71 ± 0.62	82 ± 27
Diffusing capacity (mL/min/mmHg)	8.9 ± 4.0	47 ± 16
SAC BDI	4.7 ± 1.6	

BD, bronchodilator; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; IC, inspiratory capacity; SAC BDI, self-administered computerized baseline dyspnea index.[30]

Data were obtained at visit 1. Three patients had stage II disease, 10 patients had stage III disease, and seven had grade IV disease.[28b] Medications for COPD included: short-acting beta-agonist ($n = 20$); long-acting beta-agonist ($n = 9$); anticholinergic ($n = 18$); inhaled corticosteroid ($n = 14$); and theophylline ($n = 1$).

more common for FVC than FEV1 in patients with severe emphysema.[18,19]

To our knowledge, this study is the first to compare the bronchodilator effects of inhaling similar beta-agonists via DPI and via nebulization in a unique COPD population who

TABLE 3. CHANGES IN LUNG FUNCTION FROM BASELINE

	Arformoterol	*Salmeterol*	*p value*
ΔFEV1 (mL)			
15 min	70 ± 65	37 ± 74	0.02
30 min	90 ± 74	40 ± 74	0.007
2 hr	84 ± 72 (11%)	52 ± 105 (7%)	0.17
ΔFVC (mL)			
15 min	163 ± 174	96 ± 129	0.05
30 min	228 ± 196	149 ± 212	0.19
2 hr	268 ± 218 (14%)	164 ± 245 (8%)	0.02
ΔIC (mL)			
15 min	170 ± 129	94 ± 139	0.02
30 min	181 ± 128	85 ± 126	0.01
2 hr	195 ± 154 (13%)	112 ± 126 (8%)	0.05

Δ, difference compared with baseline values; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; IC, inspiratory capacity.

Numbers in parentheses are percent change from baseline.

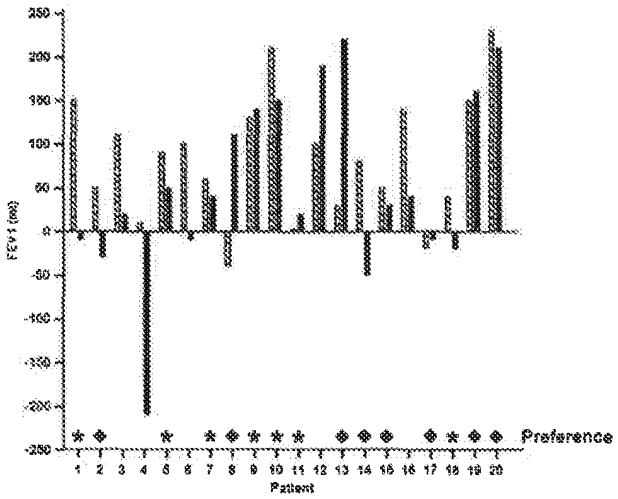

FIG. 2. Individual changes in forced expiratory volume in 1 sec (FEV1) at 2 hr compared with baseline. Hatched bars, arformoterol; solid bars, salmeterol. For the group, $p = 0.17$. *Patient preference for arformoterol; ❖patient preference for salmeterol. Five patients did not have a preference.

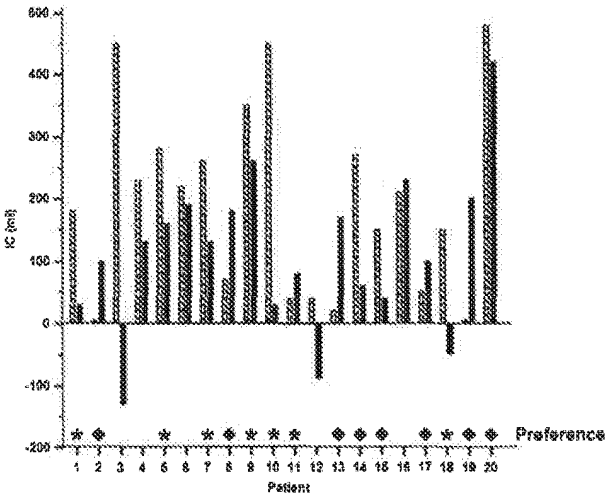

FIG. 4. Individual changes in inspiratory capacity (IC) at 2 hr compared with baseline. Hatched bars, arformoterol; solid bars, salmeterol. For the group, $p = 0.05$. *Patient preference for arformoterol; ❖patient preference for salmeterol. Five patients did not have a preference.

had a suboptimal PIFRresist. As a result, these patients may not be able to completely inhale a dry powder bronchodilator into their lower respiratory tract. The DPI and nebulizer delivery systems require different inhalational maneuvers. A deep and hard inhalation is recommended to overcome the internal resistance of a DPI in order to deaggregate the powder formulation into fine particles, whereas tidal breathing is recommended for inhalation of aerosol solution in a nebulizer.[1] We did not investigate the mechanism for greater improvement in lung function with arformoterol, but consider it likely that the nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract

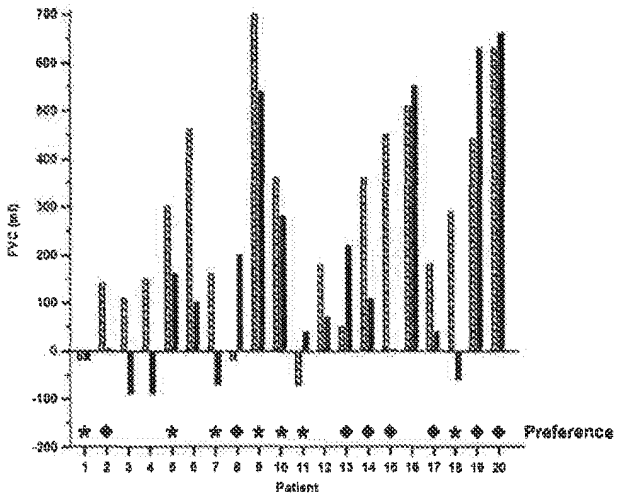

FIG. 3. Individual changes in forced vital capacity (FVC) at 2 hr compared with baseline. Hatched bars, arformoterol; solid bars, salmeterol. For the group, $p = 0.02$. *Patient preference for arformoterol; ❖patient preference for salmeterol. Five patients did not have a preference.

than dry powder salmeterol in our patients with a suboptimal PIFRresist. However, imaging studies using radiolabeled tracer material attached to the medication would be required to demonstrate this effect.[20,21]

Although we did not measure residual volume (RV) and functional residual capacity (FRC) in our patients, the reduced values for FVC and IC at baseline suggest that our patients had air trapping and hyperinflation. Improvements in FVC and IC are considered to be markers of changes in RV and FRC, respectively, after bronchodilator administration.[19,22] Newton and colleagues[23] showed substantial increases in both FVC and IC after inhalation of albuterol in hyperinflated patients with COPD even though only a minority of patients had improvements in FEV1. Although it is unknown whether the improvements in FVC and IC with arformoterol would be sufficient for our patients with PIFR of < 60 L/min to experience clinical benefit, previous studies in patients with COPD have demonstrated significant improvements in dyspnea ratings with arformoterol after 3 and 6 months.[8,10]

There are limitations to our study. First, the study was single-blind as the patient was aware which medication was administered at each test visit, although the technician collecting the outcome data was not informed of medication assignment. A double-blind condition would have been preferred to avoid potential bias. However, a placebo Diskus identical in appearance to salmeterol was not available. Second, we compared salmeterol Diskus rather than formoterol Turbuhaler with nebulized arformoterol solution, because the Diskus is a widely used DPI and has a lower internal resistance than the Turbuhaler.[2,3,13,24] In theory, a lower internal resistance, as exists with the Diskus DPI, would minimize any possible limitations of a suboptimal PIFRresist. Third, this study was performed in 20 patients, and a larger number of participants would be required to exclude a type II error. Fourth, single doses of bronchodilators were administered, and multiple doses over a longer

study period with assessment of clinical outcomes would be relevant.[25]

In 2001, a European Respiratory Society task force suggested that future research is needed to identify which patients with COPD "might benefit (or not benefit) from nebulized therapy using clinically relevant assessment systems."[26] This task force proposed optimizing the patient's inhalational technique with a DPI, and if the patient does not experience subjective benefit, then switching to nebulized therapy.[26] This approach is used commonly in clinical practice. Present guidelines and statements on the management of stable COPD do not recommend any objective measure as to when to prescribe nebulized bronchodilator therapy.[15,27–29]

Our study is the first to prospectively examine whether using a threshold of PIFRresist of <60 L/min against a specific DPI is a useful criterion for when to use a nebulizer to deliver bronchodilator medications. Our results should be interpreted with caution until supported by a prospective and double-blind study with a larger number of patients. A 1–2-week randomized controlled trial comparing dry powder and nebulized bronchodilators is needed in patients with COPD who exhibit a suboptimal PIFRresist to further address the question, "When should nebulized bronchodilator therapy be prescribed for patients with COPD?"

Acknowledgments

Dr. Mahler developed the research protocol, supervised data collection, reviewed the analysis, and prepared the manuscript. Dr. Mahler is the guarantor of the manuscript and takes responsibility for the integrity of the data and the accuracy of data analysis. Ms. Waterman assisted in the development of the research protocol, collected data, performed statistical analysis, and reviewed the manuscript. Mr. Ward assisted in the development of the research protocol, collected data, and reviewed the manuscript. Dr. Gifford reviewed and revised the research protocol, performed statistical analysis, and reviewed the manuscript. Sunovion Pharmaceuticals Inc. provided a grant for this investigator-initiated investigation to the Clinical Trials Office at Dartmouth-Hitchcock Medical Center, but had no role in the conduct of the study, data analysis, or manuscript preparation/review.

Author Disclosure Statement

Dr. Mahler serves as a consultant to Boehringer Ingelheim, Forest, GlaxoSmithKline, Novartis, and Sunovion, and serves on advisory boards of Forest, GlaxoSmithKline, Merck, Novartis, Pearl, and Sunovion. The Clinical Trials Office at Dartmouth-Hitchcock Medical Center has received grant support from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sunovion for which Dr. Mahler was the principal investigator. Ms. Waterman, Mr. Ward, and Dr. Gifford have no conflicts of interest.

References

1. Laube BL, Janssens HM, de Jongh FH, Devadason SG, Dhand R, Diot P, Everard ML, Horvath I, Navalesi P, Voshaar T, and Chrystyn H: ERS/ISAM task force report: what the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011;37:1308–1331.
2. Al-Showair RA, Tarsin WY, Assi KH, Pearson SB, and Chrystyn H: Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? Respir Med. 2007;101:2395–2401.
3. Janssens W, VandenBrande P, Hardeman E, De Langhe E, Philps T, Troosters T, and Decramer MJ: Inspiratory flow rates at different levels of resistance in elderly COPD patients. Eur Respir J. 2008;31:78–83.
4. Vincken W, Dekhuijzen PR, and Barnes P; ADMIT Group: The ADMIT series—Issues in inhalation therapy. 4) How to choose inhaler devices for the treatment of COPD. Prim Care Respir J. 2010;19:10–20.
5. Sestini P, Cappiello V, Aliani M, Martucci P, Sena A, Vaghi A, Canessa PA, Neri M, and Melani AS: Prescription bias and factors associated with improper use of inhalers. J Aerosol Med. 2006;19:127–136.
6. Mahler DA, Waterman LA, and Gifford AH: Prevalence and COPD phenotype for a suboptimal peak inspiratory flow rate against the simulated resistance of the Diskus® dry powder inhaler. J Aerosol Med Pulm Drug Deliv. 2013 [Epub ahead of print].
7. Gross NJ, Kerwin E, Levine B, Kim KT, Denis-Mize K, Hamzavi M, Carpenter M, and Rinehart M. Nebulized formoterol fumarate: dose selection and pharmacokinetics. Pulm Pharmacol Ther. 2008;21:818–823.
8. Hanania NA, Donohue JF, Nelson H, Sciarappa K, Goodwin E, Baumgartner RA, and Hanrahan JP: The safety and efficacy of arformoterol and formoterol in COPD. COPD. 2010; 7:17–31.
9. Hanrahan JP, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, and Baumgartner RA: Effect of nebulized arformoterol on airway function in COPD: results from two randomized trials. COPD. 2008;5:25–34.
10. Baumgartner RA, Hanania NA, Calhoun WJ, Sahn SA, Sciarappa K, and Hanrahan JP: Nebulized arformoterol in patients with COPD: a 12-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled trial. Clin Ther. 2007;29:261–278.
11. van der Palen J: Peak inspiratory flow through Diskus and Turbuhaler, measured by means of a peak inspiratory flow meter (In-Check DIAL). Respir Med. 2005;97:285–289.
12. Clark AR, and Hollingworth AM: The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers—implications for *in vitro* testing. J Aerosol Med. 1993;6:99–110.
13. Celli BR, and MacNee W; ATS/ERS Task Force: Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932–946.
14. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, and Wanger J: General considerations for lung function testing. Eur Respir J. 2005;26:153–161.
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, and Wanger J: Standardisation of spirometry. Eur Respir J. 2005;26: 319–338.
16. Hankinson JL, Odencrantz JR, and Fedan KB: Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159:179–187.

17. Crapo RO, Morris AH, Clayton PD, and Nixon CR: Lung volumes in healthy nonsmoking adults. Bull Eur Physiopath Respir. 1982;18:419–425.
18. Han MK, Wise R, Mumford J, Sciurba F, Criner GJ, Curtis JL, Murray S, Sternberg A, Weinman G, Kazerooni E, Fishman AP, Make B, Hoffman EA, Mosenifar Z, and Martinez FJ: Prevalence and clinical correlates of bronchoreversibility in severe emphysema. Eur Respir J. 2010;35:1048–1056.
19. O'Donnell DE, Forkert L, and Webb KA: Evaluation of bronchodilator responses in patients with "irreversible" emphysema. Eur Respir J. 2001;18:914–920.
20. Leach CL, Kuehl PJ, Chand R, Ketai L, Norenberg JP, and McDonald JD: Characterization of respiratory deposition of fluticasone-salmeterol hydrofluoroalkane-134a and hydrofluoroalkane-134a beclomethasone in asthmatic patients. Ann Allergy Asthma Immun. 2012;108:195–200.
21. Walker PS, Petterson GL, Bondesson E, and Conway JH: An advanced and detailed *in vitro* validation procedure for the radiolabeling of carrier-free terbutaline sulphate dry powder. J Aerosol Med. 2001;14:227–236.
22. Ramirez-Venegas A, Ward J, Lentine T, and Mahler DA: Salmeterol reduces dyspnea and improves lung function in patients with COPD. Chest. 1997;112:336–340.
23. Newton MF, O'Donnell DE, and Forkert L: Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest. 2002;121:1042–1050.
24. Atkins PJ: Dry powder inhalers: an overview. Respir Care. 2005;50:1304–1312.
25. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, Busasco V, Burge PS, Calverley PMA, Celli BR, Jones PW, Mahler DA, Make B, Miravitlles M, Page CP, Palango P, Parr D, Pistolesi M, Rennard SI, Rutten-van Molken MP, Stockley R, Sullivan SD, Wedzicha JA, and Wouters EF; American Thoracic Society/European Respiratory Society Task Force on outcomes of COPD: Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J. 2008;31:416–469.
26. Boe J, Dennis JH, O'Driscoll BR, Bauer TT, Carone M, Dautzenberg B, Diot P, Heslop K, and Lannefors L: European Respiratory Society Guidelines on the use of nebulizers. Eur Respir J. 2001;18:228–242.
27. Qaseem A, Wilt TJ, Weinberger SE, Snow V, Hanania NA, Criner G, van der Molen T, Marciniuk D, Denberg T, Schunemann H, Wedzicha W, MacDonald R, and Shekelle P: Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155:179–191.
28. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, Ford G, Gervais A, Goldstein R, Hodder R, Kaplan A, Keenan S, Lacasse Y, Maltais F, Road J, Rocker G, Sin D, Sinuff T, and Voduc N: Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2007 update. Can Respir J. 2007;14 Suppl B:5B–32B.
29. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, and Rodriguez-Roisin R: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD Executive Summary. Am J Respir Crit Care Med. 2013;187:347–365.
30. Mahler DA, Waterman LA, Ward J, McCusker C, ZuWallack R, and Baird JC: Validity and responsiveness of the self-administered computerized versions of the baseline and transition dyspnea indexes. Chest. 2007;132:1283–1290.

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SERIES "ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING"
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Standardisation of spirometry

M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P.M. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi and J. Wanger

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KEYWORDS: **Peak expiratory flow, spirometry, spirometry standardisation, spirometry technique, spirometry traning, ventilation**

BACKGROUND

Spirometry is a physiological test that measures how an individual inhales or exhales volumes of air as a function of time. The primary signal measured in spirometry may be volume or flow.

Spirometry is invaluable as a screening test of general respiratory health in the same way that blood pressure provides important information about general cardiovascular health. However, on its own, spirometry does not lead clinicians directly to an aetiological diagnosis. Some indications for spirometry are given in table 1.

In this document, the most important aspects of spirometry are the forced vital capacity (FVC), which is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration, and the forced expiratory volume (FEV) in one second, which is the volume delivered in the first second of an FVC manoeuvre. Other spirometric variables derived from the FVC manoeuvre are also addressed.

Spirometry can be undertaken with many different types of equipment, and requires cooperation between the subject and the examiner, and the results obtained will depend on technical as well as personal factors (fig. 1). If the variability of the results can be diminished and the measurement accuracy can be improved, the range of normal values for populations can be narrowed and abnormalities more easily detected. The Snowbird workshop held in 1979 resulted in the first American Thoracic Society (ATS) statement on the standardisation of spirometry [1]. This was updated in 1987 and again in 1994 [2, 3]. A similar initiative was undertaken by the European Community for Steel and Coal, resulting in the first European standardisation document in 1983 [4]. This was then updated in 1993 as the official statement of the European Respiratory Society (ERS) [5]. There are generally only minor differences between the two most recent ATS and ERS statements, except that the ERS statement includes absolute lung volumes and the ATS does not.

This document brings the views of the ATS and ERS together in an attempt to publish standards that can be applied more

TABLE 1 Indications for spirometry

Diagnostic
- To evaluate symptoms, signs or abnormal laboratory tests
- To measure the effect of disease on pulmonary function
- To screen individuals at risk of having pulmonary disease
- To assess pre-operative risk
- To assess prognosis
- To assess health status before beginning strenuous physical activity programmes

Monitoring
- To assess therapeutic intervention
- To describe the course of diseases that affect lung function
- To monitor people exposed to injurious agents
- To monitor for adverse reactions to drugs with known pulmonary toxicity

Disability/impairment evaluations
- To assess patients as part of a rehabilitation programme
- To assess risks as part of an insurance evaluation
- To assess individuals for legal reasons

Public health
- Epidemiological surveys
- Derivation of reference equations
- Clinical research

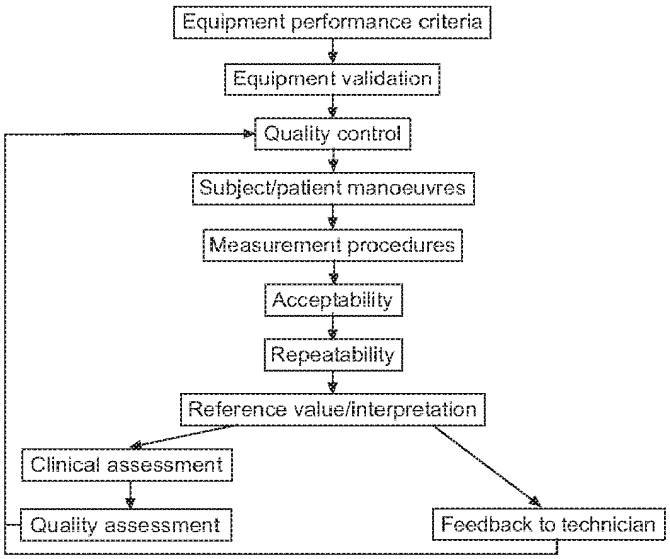

FIGURE 1. Spirometry standardisation steps.

widely. The statement is structured to cover definitions, equipment and patient-related procedures. All recording devices covered by this statement must meet the relevant requirements, regardless of whether they are for monitoring or diagnostic purposes. There is no separate category for "monitoring" devices.

Although manufacturers have the responsibility for producing pulmonary function testing systems that satisfy all the recommendations presented here, it is possible that, for some equipment, meeting all of them may not always be achievable. In these circumstances, manufacturers should clearly identify which equipment requirements have not been met. While manufacturers are responsible for demonstrating the accuracy and reliability of the systems that they sell, it is the user who is responsible for ensuring that the equipment's measurements remain accurate. The user is also responsible for following local law, which may have additional requirements. Finally, these guidelines are minimum guidelines, which may not be sufficient for all settings, such as when conducting research, epidemiological studies, longitudinal evaluations and occupational surveillance.

FEV_1 AND FVC MANOEUVRE

Definitions

FVC is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration, *i.e.* vital capacity performed with a maximally forced expiratory effort, expressed in litres at body temperature and ambient pressure saturated with water vapour (BTPS; see *BTPS correction* section).

FEV_1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in litres at BTPS.

Equipment

Requirements

The spirometer must be capable of accumulating volume for $\geq$15 s (longer times are recommended) and measuring volumes of $\geq$8 L (BTPS) with an accuracy of at least $\pm$3% of reading or $\pm$0.050 L, whichever is greater, with flows between 0 and 14 $L \cdot s^{-1}$. The total resistance to airflow at 14.0 $L \cdot s^{-1}$ must be <1.5 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ (0.15 $kPa \cdot L^{-1} \cdot s^{-1}$; see *Minimal recommendations for spirometry systems* section). The total resistance must be measured with any tubing, valves, pre-filter, *etc.* included that may be inserted between the subject and the spirometer. Some devices may exhibit changes in resistance due to water vapour condensation, and accuracy requirements must be met under BTPS conditions for up to eight successive FVC manoeuvres performed in a 10-min period without inspiration from the instrument.

Display

For optimal quality control, both flow–volume and volume–time displays are useful, and test operators should visually inspect the performance of each manoeuvre for quality assurance before proceeding with another manoeuvre. This inspection requires tracings to meet the minimum size and resolution requirements set forth in this standard.

Displays of flow *versus* volume provide more detail for the initial portion (first 1 s) of the FVC manoeuvre. Since this portion of the manoeuvre, particularly the peak expiratory flow (PEF), is correlated with the pleural pressure during the manoeuvre, the flow–volume display is useful to assess the magnitude of effort during the initial portions of the manoeuvre. The ability to overlay a series of flow–volume curves registered at the point of maximal inhalation may be helpful in evaluating repeatability and detecting submaximal efforts. However, if the point of maximal inhalation varies between blows, then the interpretation of these results is difficult because the flows at identical measured volumes are being achieved at different absolute lung volumes. In contrast, display of the FVC manoeuvre as a volume–time graph provides more detail for the latter part of the manoeuvre. A volume–time tracing of sufficient size also allows independent measurement and calculation of parameters from the FVC manoeuvres. In a display of multiple trials, the sequencing of the blows should be apparent to the user.

For the start of test display, the volume–time display should include $\geq$0.25 s, and preferably 1 s, before exhalation starts (zero volume). This time period before there is any change in volume is needed to calculate the back extrapolated volume (EV; see *Start of test criteria* section) and to evaluate effort during the initial portion of the manoeuvre. Time zero, as defined by EV, must be presented as the zero point on the graphical output.

The last 2 s of the manoeuvre should be displayed to indicate a satisfactory end of test (see *End of test criteria* section).

When a volume–time curve is plotted as hardcopy, the volume scale must be $\geq$10 $mm \cdot L^{-1}$ (BTPS). For a screen display, 5 $mm \cdot L^{-1}$ is satisfactory (table 2).

The time scale should be $\geq$20 $mm \cdot s^{-1}$, and larger time scales are preferred ($\geq$30 $mm \cdot s^{-1}$) when manual measurements are made [1, 6, 7]. When the volume–time plot is used in conjunction with a flow–volume curve (*i.e.* both display methods are provided for interpretations and no hand

TABLE 2 Recommended minimum scale factors for time, volume and flow on graphical output

Parameter	Instrument display		Hardcopy graphical output	
	Resolution required	Scale factor	Resolution required	Scale factor
Volume#	0.050 L	5 mm·L^{-1}	0.025 L	10 mm·L^{-1}
Flow#	0.200 L·s^{-1}	2.5 mm·L^{-1}·s^{-1}	0.100 L·s^{-1}	5 mm·L^{-1}·s^{-1}
Time	0.2 s	10 mm·s^{-1}	0.2 s	20 mm·s^{-1}

#: the correct aspect ratio for a flow *versus* volume display is two units of flow per one unit of volume.

TABLE 3 Summary of equipment quality control

Test	Minimum interval	Action
Volume	Daily	Calibration check with a 3-L syringe
Leak	Daily	3 cmH_2O (0.3 kPa) constant pressure for 1 min
Volume linearity	Quarterly	1-L increments with a calibrating syringe measured over entire volume range
Flow linearity	Weekly	Test at least three different flow ranges
Time	Quarterly	Mechanical recorder check with stopwatch
Software	New versions	Log installation date and perform test using "known" subject

measurements are performed), the time scale requirement is reduced to 10 mm·s^{-1} from the usually required minimum of 20 mm·s^{-1} (table 2). The rationale for this exception is that the flow–volume curve can provide the means for quality assessment during the initial portion of the FVC manoeuvre. The volume–time curve can be used to evaluate the latter part of the FVC manoeuvre, making the time scale less critical.

Validation

It is strongly recommended that spirometry systems should be evaluated using a computer-driven mechanical syringe or its equivalent, in order to test the range of exhalations that are likely to be encountered in the test population. Testing the performance of equipment is not part of the usual laboratory procedures (see *Test signals for spirometer testing* section).

Quality control

Attention to equipment quality control and calibration is an important part of good laboratory practice. At a minimum, the requirements are as follows: 1) a log of calibration results is maintained; 2) the documentation of repairs or other alterations which return the equipment to acceptable operation; 3) the dates of computer software and hardware updates or changes; and 4) if equipment is changed or relocated (*e.g.* industrial surveys), calibration checks and quality-control procedures must be repeated before further testing begins.

Key aspects of equipment quality control are summarised in table 3.

Calibration is the procedure for establishing the relationship between sensor-determined values of flow or volume and the actual flow or volume.

A calibration check is different from calibration and is the procedure used to validate that the device is within calibration limits, *e.g.* ±3% of true. If a device fails its calibration check, then a new calibration procedure or equipment maintenance is required. Calibration checks must be undertaken daily, or more frequently, if specified by the manufacturer.

The syringe used to check the volume calibration of spirometers must have an accuracy of ±15 mL or ±0.5% of the full scale (15 mL for a 3-L syringe), and the manufacturer must provide recommendations concerning appropriate intervals between syringe calibration checks. Users should be aware that a syringe with an adjustable or variable stop may be out of calibration if the stop is reset or accidentally moved. Calibration syringes should be periodically (*e.g.* monthly) leak tested at more than one volume up to their maximum; this can be done by attempting to empty them with the outlet corked. A dropped or damaged syringe should be considered out of calibration until it is checked.

With regard to time, assessing mechanical recorder time scale accuracy with a stopwatch must be performed at least quarterly. An accuracy of within 2% must be achieved.

Quality control for volume-measuring devices

The volume accuracy of the spirometer must be checked at least daily, with a single discharge of a 3-L calibrated syringe. Daily calibration checking is highly recommended so that the onset of a problem can be determined within 1 day, and also to help define day-to-day laboratory variability. More frequent checks may be required in special circumstances, such as: 1) during industrial surveys or other studies in which a large number of subject manoeuvres are carried out, the equipment's calibration should be checked more frequently than daily [8]; and 2) when the ambient temperature is changing (*e.g.* field studies), volume accuracy must be checked more frequently than daily and the BTPS correction factor appropriately updated.

The accuracy of the syringe volume must be considered in determining whether the measured volume is within acceptable limits. For example, if the syringe has an accuracy of 0.5%, a reading of ±3.5% is appropriate.

The calibration syringe should be stored and used in such a way as to maintain the same temperature and humidity of the testing site. This is best accomplished by keeping the syringe in close proximity to the spirometer, but out of direct sunlight and away from heat sources.

Volume-type spirometer systems must be evaluated for leaks every day [9, 10]. The importance of undertaking this daily test cannot be overstressed. Leaks can be detected by applying a constant positive pressure of ⩾3.0 cmH_2O (0.3 kPa) with the spirometer outlet occluded (preferably at or including the mouthpiece). Any observed volume loss >30 mL after 1 min indicates a leak [9, 10] and needs to be corrected.

At least quarterly, volume spirometers must have their calibration checked over their entire volume range using a calibrated syringe [11] or an equivalent volume standard. The measured volume should be within ±3.5% of the reading or 65 mL, whichever is greater. This limit includes the 0.5% accuracy limit for a 3-L syringe. The linearity check procedure provided by the manufacturer can be used if it is equivalent to one of the following procedures: 1) consecutive injections of 1-L volume increments while comparing observed volume with the corresponding cumulative measured volume, *e.g.* 0–1, 1–2, 2–3,…6–7 and 7–8 L, for an 8-L spirometer; and 2) injection of a 3-L volume starting at a minimal spirometer volume, then repeating this with a 1-L increment in the start position, *e.g.* 0–3, 1–4, 2–5, 3–6, 4–7 and 5–8 L, for an 8-L spirometer.

The linearity check is considered acceptable if the spirometer meets the volume accuracy requirements for all volumes tested.

Quality control for flow-measuring devices

With regards to volume accuracy, calibration checks must be undertaken at least daily, using a 3-L syringe discharged at least three times to give a range of flows varying between 0.5 and 12 $L \cdot s^{-1}$ (with 3-L injection times of ~6 s and <0.5 s). The volume at each flow should meet the accuracy requirement of ±3.5%. For devices using disposable flow sensors, a new sensor from the supply used for patient tests should be tested each day.

For linearity, a volume calibration check should be performed weekly with a 3-L syringe to deliver three relatively constant flows at a low flow, then three at a mid-range flow and finally three at a high flow. The volumes achieved at each of these flows should each meet the accuracy requirement of ±3.5%.

Test procedure

There are three distinct phases to the FVC manoeuvre, as follows: 1) maximal inspiration; 2) a "blast" of exhalation; and 3) continued complete exhalation to the end of test (EOT).

The technician should demonstrate the appropriate technique and follow the procedure described in table 4. The subject should inhale rapidly and completely from functional residual capacity (FRC), the breathing tube should be inserted into the subject's mouth (if this has not already been done), making sure the lips are sealed around the mouthpiece and that the tongue does not occlude it, and then the FVC manoeuvre should be begun with minimal hesitation. Reductions in PEF and FEV_1 have been shown when inspiration is slow and/or there is a 4–6 s pause at total lung capacity (TLC) before beginning exhalation [12]. It is, therefore, important that the preceding inspiration is fast and any pause at full inspiration be minimal (*i.e.* only for 1–2 s). The test assumes a full inhalation before beginning the forced exhalation, and it is imperative that the subject takes a complete inhalation before beginning the manoeuvre. The subject should be prompted to "blast," not just "blow," the air from their lungs, and then he/she should be encouraged to fully exhale. Throughout the manoeuvre, enthusiastic coaching of the subject using appropriate body language and phrases, such as "keep going", is required. It is particularly helpful to observe the subject with occasional glances to check for distress, and to observe the tracing or computer display during the test to help ensure maximal effort. If the patient feels "dizzy", the manoeuvre should be stopped, since syncope could follow due to prolonged interruption of venous return to the thorax. This is more likely to occur in older subjects and those with airflow limitation. Performing a vital capacity (VC) manoeuvre (see *VC and IC manoeuvre* section), instead of obtaining FVC, may help to avoid syncope in some subjects. Reducing the effort partway through the manoeuvre [13] may give a higher expiratory volume in some subjects, but then is no longer a maximally forced expiration. Well-fitting false teeth should not be routinely removed, since they preserve oropharyngeal geometry and spirometry results are generally better with them in place [14].

With appropriate coaching, children as young as 5 yrs of age are often able to perform acceptable spirometry [15]. The technicians who are involved in the pulmonary function testing of children should be specifically trained to deal with such a situation. A bright, pleasant atmosphere,

TABLE 4 Procedures for recording forced vital capacity

- **Check the spirometer calibration**
- **Explain the test**
- **Prepare the subject**
  - Ask about smoking, recent illness, medication use, *etc.*
  - Measure weight and height without shoes
- **Wash hands**
- **Instruct and demonstrate the test to the subject, to include**
  - Correct posture with head slightly elevated
  - Inhale rapidly and completely
  - Position of the mouthpiece (open circuit)
  - Exhale with maximal force
- **Perform manoeuvre (closed circuit method)**
  - Have subject assume the correct posture
  - Attach nose clip, place mouthpiece in mouth and close lips around the mouthpiece
  - Inhale completely and rapidly with a pause of <1 s at TLC
  - Exhale maximally until no more air can be expelled while maintaining an upright posture
  - Repeat instructions as necessary, coaching vigorously
  - Repeat for a minimum of three manoeuvres; no more than eight are usually required
  - Check test repeatability and perform more manoeuvres as necessary
- **Perform manoeuvre (open circuit method)**
  - Have subject assume the correct posture
  - Attach nose clip
  - Inhale completely and rapidly with a pause of <1 s at TLC
  - Place mouthpiece in mouth and close lips around the mouthpiece
  - Exhale maximally until no more air can be expelled while maintaining an upright posture
  - Repeat instructions as necessary, coaching vigorously
  - Repeat for a minimum of three manoeuvres; no more than eight are usually required
  - Check test repeatability and perform more manoeuvres as necessary

TLC: total lung capacity

including age-appropriate toys, reading material and art, is important in making children feel at ease. Encouragement, detailed but simple instructions, lack of intimidation and visual feedback in the teaching are important in helping children to perform the manoeuvre. Even if unsuccessful at the first session, children will learn to be less intimidated and may perform far better in a subsequent session. Testing children in "adult" laboratories, where no effort is made to cater for the specific needs of the younger subjects, is to be discouraged.

The use of a nose clip or manual occlusion of the nares is recommended, and, for safety reasons, testing should be preferably done in the sitting position, using a chair with arms and without wheels. If testing is undertaken with the patient standing or in another position, this must be documented on the report.

Within-manoeuvre evaluation

Start of test criteria

The start of test, for the purpose of timing, is determined by the back extrapolation method (fig. 2) [1, 3, 9, 16]. The new "time zero" from back extrapolation defines the start for all timed measurements. For manual measurements, the back extrapolation method traces back from the steepest slope on the volume–time curve [17]. For computerised back extrapolation, it is recommended that the largest slope averaged over an 80-ms period is used [18]. Figure 2 provides an example and explanation of back extrapolation and the derivation of EV. To achieve an accurate time zero and assure the FEV_1 comes from a maximal effort curve, the EV must be <5% of the FVC or 0.150 L, whichever is greater. If a manoeuvre has an obviously hesitant start, the technician may terminate the trial early to avoid an unnecessary prolonged effort.

Rapid computerised feedback to the technician when the start criteria are not met is strongly encouraged. In addition to the expiratory manoeuvre, the volume-time curve display (graph)

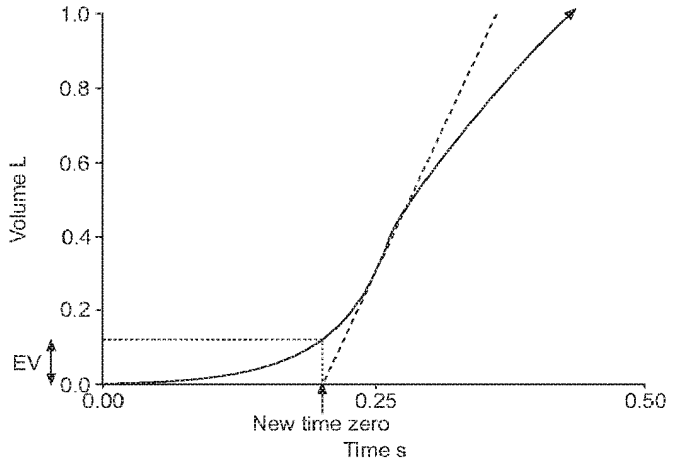

FIGURE 2. Expanded version of the early part of a subject's volume–time spirogram, illustrating back extrapolation through the steepest part of the curve, where flow is peak expiratory flow (PEF), to determine the new "time zero". Forced vital capacity (FVC)=4.291 L; back extrapolated volume (EV)=0.123 L (2.9% FVC). -----: back extrapolation line through PEF.

should ideally include the whole preceding inspiratory manoeuvre, but must include ⩾0.25 s and preferably ⩾1 s prior to the start of exhalation (time zero). The equipment should display the EV value. Inspection of the flow–volume curve may be added as a measure of the satisfactory start of test. PEF should be achieved with a sharp rise and occur close to the point of maximal inflation, *i.e.* the start of exhalation (see *Equipment* section).

End of test criteria

It is important for subjects to be verbally encouraged to continue to exhale the air at the end of the manoeuvre to obtain optimal effort, *e.g.* by saying "keep going". EOT criteria are used to identify a reasonable FVC effort, and there are two recommended EOT criteria, as follows. 1) The subject cannot or should not continue further exhalation. Although subjects should be encouraged to achieve their maximal effort, they should be allowed to terminate the manoeuvre on their own at any time, especially if they are experiencing discomfort. The technician should also be alert to any indication that the patient is experiencing discomfort, and should terminate the test if a patient is becoming uncomfortable or is approaching syncope. 2) The volume–time curve shows no change in volume (<0.025 L) for ⩾1 s, and the subject has tried to exhale for ⩾3 s in children aged <10 yrs and for ⩾6 s in subjects aged >10 yrs.

The equipment should signal to the technician if the plateau criteria were not met. A satisfactory EOT may still have been achieved, but an equipment alert will help the technician to pinpoint where the subject may need more encouragement. It is of note that a closure of the glottis may prematurely terminate a manoeuvre at <6 s, even when the apparent duration of the blow exceeds 6 s.

For patients with airways obstruction or older subjects, exhalation times of >6 s are frequently needed. However, exhalation times of >15 s will rarely change clinical decisions. Multiple prolonged exhalations are seldom justified and may cause light headedness, syncope, undue fatigue and unnecessary discomfort.

Achieving EOT criteria is one measure of manoeuvre acceptability. Manoeuvres that do not meet EOT criteria should not be used to satisfy the requirement of three acceptable manoeuvres. However, early termination, by itself, is not a reason to eliminate all the results from such a manoeuvre from further consideration. Information such as the FEV_1 may be useful (depending on the length of exhalation) and can be reported from these early terminated manoeuvres.

Some young children may have difficulty meeting the ATS EOT criteria [3], although they may meet other repeatability criteria [19]. Curve-fitting techniques [20] may prove useful in developing new EOT criteria specific for young children.

Additional criteria

A cough during the first second of the manoeuvre can affect the measured FEV_1 value. Coughing in the first second or any other cough that, in the technician's judgment, interferes with the measurement of accurate results [3] will render a test unacceptable.

A Valsalva manoeuvre (glottis closure) or hesitation during the manoeuvre that causes a cessation of airflow in a manner that precludes an accurate estimate of either FEV1 or FVC [3] will render a test unacceptable.

There must be no leak at the mouth [3]. Patients with neuromuscular disease may require manual or other assistance from the technician to guarantee an adequate seal.

Obstruction of the mouthpiece, *e.g.* by the tongue being placed in front of the mouthpiece or by teeth in front of the mouthpiece, or by distortion from biting, may affect the performance of either the device or the subject.

Summary of acceptable blow criteria

The acceptability criteria are a satisfactory start of test and a satisfactory EOT, *i.e.* a plateau in the volume–time curve. In addition, the technician should observe that the subject understood the instructions and performed the manoeuvre with a maximum inspiration, a good start, a smooth continuous exhalation and maximal effort. The following conditions must also be met: 1) without an unsatisfactory start of expiration, characterised by excessive hesitation or false start extrapolated volume or EV >5% of FVC or 0.150 L, whichever is greater (fig. 2); 2) without coughing during the first second of the manoeuvre, thereby affecting the measured FEV1 value, or any other cough that, in the technician's judgment, interferes with the measurement of accurate results [3]; 3) without early termination of expiration (see *End of test criteria* section); 4) without a Valsalva manoeuvre (glottis closure) or hesitation during the manoeuvre that causes a cessation of airflow, which precludes accurate measurement of FEV1 or FVC [3]; 5) without a leak [3]; 6) without an obstructed mouthpiece (*e.g.* obstruction due to the tongue being placed in front of the mouthpiece, or teeth in front of the mouthpiece, or mouthpiece deformation due to biting); and 7) without evidence of an extra breath being taken during the manoeuvre.

It should be noted that a usable curve must only meet conditions 1 and 2 above, while an acceptable curve must meet all of the above seven conditions.

It is desirable to use a computer-based system that provides feedback to the technician when the above conditions are not met. The reporting format should include qualifiers indicating the acceptability of each manoeuvre. However, failure to meet these goals should not necessarily prevent reporting of results, since, for some subjects, this is their best performance. Records of such manoeuvres should be retained since they may contain useful information.

Between-manoeuvre evaluation

Using the previously described criteria, an adequate test requires a minimum of three acceptable FVC manoeuvres. Acceptable repeatability is achieved when the difference between the largest and the next largest FVC is $\leq$0.150 L and the difference between the largest and next largest FEV1 is $\leq$0.150 L [21]. For those with an FVC of $\leq$1.0 L, both these values are 0.100 L. If these criteria are not met in three manoeuvres, additional trials should be attempted, up to, but usually no more than, eight manoeuvres. Large variability among tests is often due to incomplete inhalations. Some patients may require a brief rest period between manoeuvres. Volume–time or flow–volume curves from at least the best three FVC manoeuvres must be retained. Table 5 gives a summary of the within- and between-manoeuvre evaluation.

Manoeuvre repeatability

For FVC measurements, acceptability must be determined by ascertaining that the recommendations outlined previously on performing the FVC test are met. The guidelines of the ATS [3] contain examples of unacceptable volume–time and corresponding flow–volume curves. Figure 3 shows a flow chart outlining how the criteria for blow acceptability are applied before those for repeatability.

The repeatability criteria are used to determine when more than three acceptable FVC manoeuvres are needed; these criteria are not to be used to exclude results from reports or to exclude subjects from a study. Labelling results as being derived from data that do not conform to the repeatability criteria described previously is recommended. In addition, the repeatability criteria are minimum requirements. Many subjects are able to achieve FVC and FEV1 repeatability to within 0.150 L. Manoeuvres with an unacceptable start of test or a cough (unusable curve) must be discarded before applying the repeatability criteria and cannot be used in determining the best values. Manoeuvres with early termination or a Valsalva manoeuvre may be used for selecting the largest FVC and FEV1.

TABLE 5 Summary of within- and between-manoeuvre acceptability criteria

Within-manoeuvre criteria
- Individual spirograms are "acceptable" if
  - They are free from artefacts [3]
    - Cough during the first second of exhalation
    - Glottis closure that influences the measurement
    - Early termination or cut-off
    - Effort that is not maximal throughout
    - Leak
    - Obstructed mouthpiece
  - They have good starts
    - Extrapolated volume <5% of FVC or 0.15 L, whichever is greater
  - They show satisfactory exhalation
    - Duration of ≥6 s (3 s for children) or a plateau in the volume–time curve or
      - If the subject cannot or should not continue to exhale

Between-manoeuvre criteria
- After three acceptable spirograms have been obtained, apply the following tests
  - The two largest values of FVC must be within 0.150 L of each other
  - The two largest values of FEV1 must be within 0.150 L of each other
- If both of these criteria are met, the test session may be concluded
- If both of these criteria are not met, continue testing until
  - Both of the criteria are met with analysis of additional acceptable spirograms or
  - A total of eight tests have been performed (optional) or
  - The patient/subject cannot or should not continue
- Save, as a minimum, the three satisfactory manoeuvres

FVC: forced vital capacity; FEV1: forced expiratory volume in one second

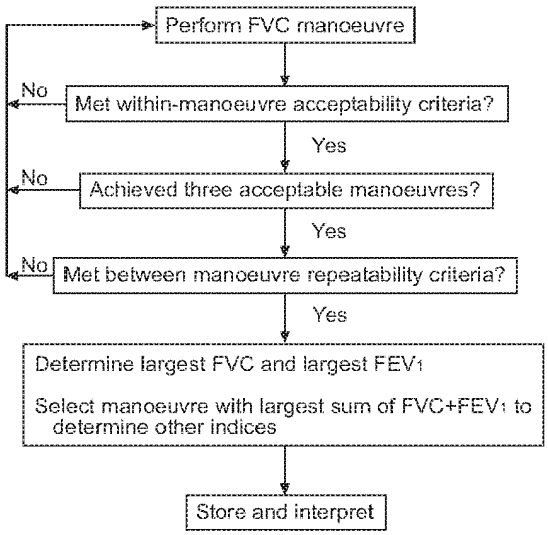

FIGURE 3. Flow chart outlining how acceptability and reapeatability criteria are to be applied. FVC: forced vital capacity; FEV1: forced expiratory volume in one second.

No spirogram or test result should be rejected solely on the basis of its poor repeatability. The repeatability of results should be considered at the time of interpretation. The use of data from manoeuvres with poor repeatability or failure to meet the EOT requirements is left to the discretion of the interpreter.

Maximum number of manoeuvres

Although there may be some circumstances in which more than eight consecutive FVC manoeuvres may be needed, eight is generally a practical upper limit for most subjects [22, 23]. After several forced expiratory manoeuvres, fatigue can begin to take its toll on subjects and additional manoeuvres would be of little added value. In extremely rare circumstances, subjects may show a progressive reduction in FEV1 or FVC with each subsequent blow. If the cumulative drop exceeds 20% of start value, the test procedure should be terminated in the interest of patient safety. The sequence of the manoeuvres should be recorded.

Test result selection

FVC and FEV1 should be measured from a series of at least three forced expiratory curves that have an acceptable start of test and are free from artefact, such as a cough (*i.e.* "usable curves"). The largest FVC and the largest FEV1 (BTPS) should be recorded after examining the data from all of the usable curves, even if they do not come from the same curve.

Other derived indices

FEV_t

FEV_t is the maximal volume exhaled by time t seconds (timed from the time zero defined by back extrapolation) of a forced expiration from a position of full inspiration, expressed in litres at BTPS. Very young children may not be able to produce prolonged expirations, but there is increasing evidence that indices derived from blows with forced expiratory times of <1 s may have clinical usefulness [19]. At present, there are insufficient data to recommend the use of $FEV_{0.5}$ or $FEV_{0.75}$.

When the subject does not exhale completely, the volume accumulated over a shorter period of time (*e.g.* 6 s) may be used as an approximate surrogate for FVC. When such surrogates are used, the volume label should reflect the shorter exhalation time (*e.g.* FEV_6 for a 6-s exhalation). FEV_6 has been increasingly considered a reasonably reliable surrogate for FVC [24] and can be used for normalising FEV_1 (*e.g.* FEV_1/FEV_6). Recording FEV_6 seems to have the advantage of being more reproducible than FVC, being less physically demanding for patients and providing a more explicit EOT. Confirmation from other studies is required.

Standardisation of FEV_1 for expired volume, FEV_1/FVC and FEV_1/VC

In some patients, a slow or unforced VC or inspiratory vital capacity (IVC) manoeuvre (see *VC and IC manoeuvre* section) may provide a larger and more appropriate denominator for calculation of the FEV_1/VC%. Some investigators have reported that the VC is slightly higher than the FVC in normal subjects [25].

$FEF_{25-75\%}$

The mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25-75\%}$) has also been known as the maximum mid-expiratory flow. This index is taken from the blow with the largest sum of FEV1 and FVC. The $FEF_{25-75\%}$ must be measured with an accuracy of at least $\pm 5\%$ of reading or ± 0.200 $L \cdot s^{-1}$ whichever is greater, over a range of up to 7 $L \cdot s^{-1}$. It should be noted that it is highly dependent on the validity of the FVC measurement and the level of expiratory effort.

PEF

PEF is usually obtained from flow–volume curve data. It is the maximum expiratory flow achieved from a maximum forced expiration, starting without hesitation from the point of maximal lung inflation, expressed in $L \cdot s^{-1}$. When PEF is recorded using a patient-administered portable PEF meter, it is often expressed in $L \cdot min^{-1}$. PEF is covered in more detail later.

Maximal expiratory flow–volume loops

The shape of a maximum flow–volume loop (MFVL), which includes forced inspiratory manoeuvres, can be helpful in quality control and in detecting the presence of upper airway obstruction. None of the numerical indices from a MFVL has clinical utility superior to FEV_1, FVC, $FEF_{25-75\%}$ and PEF, and are not considered in detail here.

Definitions

With regard to instantaneous flows, the recommended measure is the instantaneous forced expiratory flow when X% of the FVC has been expired ($FEF_{X\%}$). The maximal instantaneous forced expiratory flow when X% of the FVC remains to be expired ($MEF_{X\%}$) was the term previously recommended in Europe.

Instantaneous forced inspiratory flow when X% of the FVC has been expired ($FIF_{X\%}$) and mid-inspiratory flow when X% of the FVC has been expired refer to the flows measured on the inspiratory limb of a flow–volume loop. $FIF_{25-75\%}$, also

referred to as maximal mid-inspiratory flow, is analogous to $FEF_{25-75\%}$ (see *Other derived indices* section).

Equipment

Instantaneous flows must be measured with an accuracy of ±5% of reading or ±0.200 $L \cdot s^{-1}$, whichever is greater, over a range of -14–14 $L \cdot s^{-1}$. The level of minimum detectable flow should be 0.025 $L \cdot s^{-1}$. When a maximum flow–volume loop is plotted or displayed, exhaled flow must be plotted upwards, and exhaled volume towards the right. A 2:1 ratio must be maintained between the flow and volume scales, *e.g.* 2 $L \cdot s^{-1}$ of flow and 1 L of exhaled volume must be the same distance on their respective axes. The flow and volume scales, used in reviewing test performance, must be equivalent to that shown in table 2.

Test procedure

The subject has to make a full expiratory and inspiratory loop as a single manoeuvre. In many laboratories, this is the primary manoeuvre for spirometry. The subject is asked to take a rapid full inspiration to TLC from room air through the mouth, then insert the mouthpiece and, without hesitation, perform an expiration with maximum force until no more gas can be expelled, followed by a quick maximum inspiration. At this point, the manoeuvre is finished.

An alternative procedure is for the subject to insert the mouthpiece while undertaking tidal breathing at FRC, and then, in one continuous sequence, do the following: make a slow expiration to residual volume (RV); followed directly by a slow inspiration to TLC; follow this by a rapid full expiration with maximal effort to RV; and followed by a rapid full inspiration with maximal effort back to TLC.

This procedure is slightly more complicated and may not be suitable for all equipment, but it obtains a measurement of VC as well as FVC.

Within- and between-manoeuvre evaluation

These evaluations are the same as for FVC (see *Within-manoeuvre evaluation* and *Between-manoeuvre evaluation* sections). Occasionally, a subject is unable to perform a satisfactory inspiratory limb immediately following a maximal forced expiratory manoeuvre. This is particularly common in the elderly and the infirm. In these circumstances, it may be necessary for the subject to record an inspiratory manoeuvre separately from the expiratory manoeuvre. Equipment should be able to perform these separately and then present three or more loops together on a graphical display or output.

Flow–volume loop examples

The following figures (figures 4–10) give typical examples of commonly encountered flow–volume loop configurations. The advantages of visual pattern recognition from the MFVL can readily be appreciated. The shapes of the manoeuvres must be repeatable (fig. 10) for any interpretation to be made. This is especially true for the plateau effect on expiratory and inspiratory limbs of the manoeuvre found in upper airway obstruction, as this can be mimicked by poor effort, which is usually variable from blow to blow. A further explanation is given in the ATS/ERS statement on lung function interpretation [26].

Reversibility testing

A determination of airflow-limitation reversibility with drug administration is commonly undertaken as part of lung function testing. The choice of drug, dose and mode of delivery is a clinical decision depending on what the clinician wishes to learn from the test.

If the aim of the test is to determine whether the patient's lung function can be improved with therapy in addition to their regular treatment, then the subject can continue with his/her regular medication prior to the test.

If the clinician wants to determine whether there is any evidence of reversible airflow limitation, then the subject should undergo baseline function testing when not taking any drugs prior to the test. Short-acting inhaled drugs (*e.g.* the β-agonist albuterol/salbutamol or the anticholinergic agent ipratropium bromide) should not be used within 4 h of testing. Long-acting β-agonist bronchodilators (*e.g.* salmeterol or formoterol) and oral therapy with aminophylline or slow-release β-agonists should be stopped for 12 h prior to the test. Smoking should be avoided for ⩾1 h prior to testing and throughout the duration of the test procedure.

Method

The following steps are undertaken. 1) The subject has three acceptable tests of FEV_1, FVC and PEF recorded as described previously. 2) The drug is administered in the dose and by the method indicated for the test. For example, after a gentle and incomplete expiration, a dose of 100 μg of albuterol/salbutamol is inhaled in one breath to TLC from a valved spacer device. The breath is then held for 5–10 s before the subject exhales. Four separate doses (total dose 400 μg) are delivered at ~30-s intervals. This dose ensures that the response is high on the albuterol dose–response curve. A lower dose can be used if there is concern about any effect on the patient's heart rate or tremor. Other drugs can also be used. For the anticholinergic agent ipratropium bromide, the total dose is 160 μg (4 × 40 μg).

Three additional acceptable tests are recorded ⩾10 min and up to 15 min later for short-acting β_2-agonists, and 30 min later for short-acting anticholinergic agents.

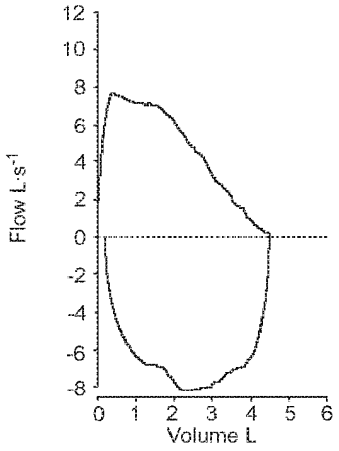

FIGURE 4. Flow–volume loop of a normal subject.

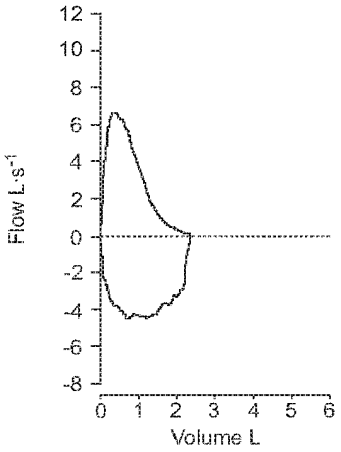

FIGURE 5. Flow–volume loop of a normal subject with end expiratory curvilinearity, which can be seen with ageing.

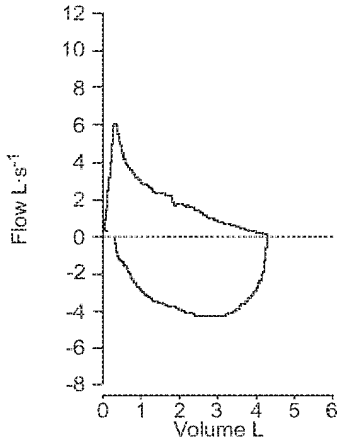

FIGURE 6. Moderate airflow limitation in a subject with asthma.

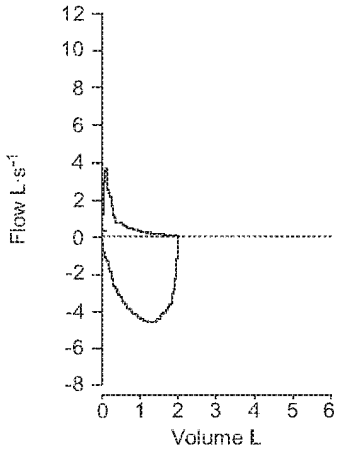

FIGURE 7. Severe airflow limitation in a subject with chronic obstructive pulmonary disease.

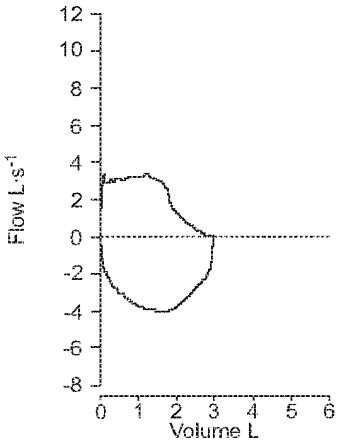

FIGURE 8. Variable intra-thoracic upper airway obstruction.

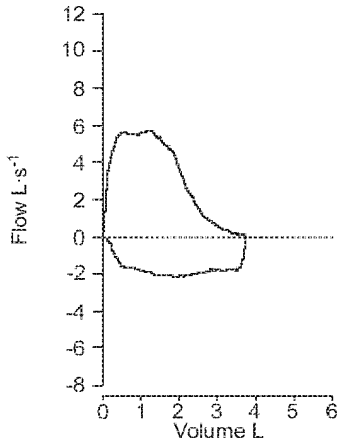

FIGURE 9. Variable extra-thoracic upper airway obstruction.

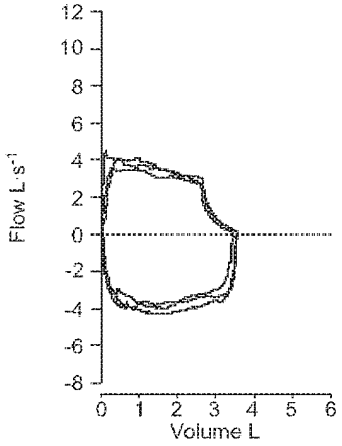

FIGURE 10. Fixed upper airway obstruction shown by three manoeuvres.

Comment on dose and delivery method

Standardising the bronchodilator dose administered is necessary in order to standardise the definition of a significant bronchodilator response. The rate of pulmonary deposition of a drug with tidal breathing from an unvented nebuliser will depend on drug concentration, rate of nebuliser output, particle-size distribution, and the ratio of the time spent in inspiration over the total respiratory time (t_i/t_{tot}) [27]. The fraction of the aerosol carried in particles with a diameter of $\leqslant 5$ μm that is expected to deposit in adult lungs if inhaled through a mouthpiece [28] is defined as the respirable fraction (RF). For example, 2.5 mg of salbutamol (albuterol) in 2.5 mL of solution, placed in a Hudson Updraft II (Hudson RCI, Temecula, CA, USA) driven by a PulmoAide compressor (De Vilbiss, Somerset, PA, USA), would produce ~0.1 mg·min^{-1} in the RF. For a respiratory rate of 15 breaths·min^{-1} and a t_i/t_{tot} of 0.45, this would give ~3 μg deposited in the lungs per breath, or 45 μg·min^{-1}. For adults using a metered dose inhaler (MDI) with a valve-holding chamber (spacer), between 10 and 20% [29, 30] of a 100-μg "puff" (or ~15 μg per activation) would be expected to be deposited in the lung of an adult. Without a spacer, the deposition will be less, and heavily technique dependent [31]. Pulmonary deposition from dry-powder inhalers is device specific, and breath-enhanced nebulisers deposit much more than unvented ones [32, 33]. CFC-free MDIs produce a smaller particle-size distribution and improved (up to 50% of dose) lung deposition compared with those with CFC propellant [34]. For children, pulmonary deposition is less than that in adults [35], possibly relating to the size of the upper airway. Each laboratory should be familiar with the pulmonary-deposition characteristics of the devices they use.

Determination of reversibility

This aspect is covered in detail in the interpretative strategy document of the ATS and ERS [26].

VC AND IC MANOEUVRE

Definitions

VC and IVC

The VC is the volume change at the mouth between the position of full inspiration and complete expiration, expressed in litres at BTPS. The slow VC can be derived in two ways. The expiratory vital capacity (EVC) is the maximal volume of air exhaled from the point of maximal inhalation. The IVC is the maximal volume of air inhaled from the point of maximal exhalation, achieved by a slow expiration from end-tidal inspiration. These manoeuvres are unforced, except at the point of reaching RV or TLC, respectively, where extra effort is required [36].

IC

Inspiratory capacity (IC) is volume change recorded at the mouth when taking a slow full inspiration with no hesitation, from a position of passive end-tidal expiration, *i.e.* FRC, to a position of maximum inspiration, expressed in litres at BTPS. IC is an indirect estimate of the degree of lung hyperinflation at rest, and is useful to assess changes in FRC with pharmacological interventions and physical exercise [37–41].

Equipment

For measurements of VC and IC, the spirometer or flow meter must comply with the requirements for FVC (as described previously) and be capable of accumulating volume for $\geqslant$30 s.

Expiratory manoeuvres or, ideally, both inspiratory and expiratory manoeuvres should be included in the display of VC manoeuvre. Regardless of whether the inspiratory or expiratory manoeuvre is used for deriving measurements, a display of the entire recorded VC manoeuvre must be provided. The maximal expiratory volume must be assessed to determine whether the subject has obtained a plateau in the expiratory effort. For display of the slow VC, the time scale may be reduced to 5 mm·s^{-1}.

Test procedure

VC

VC can be measured using conventional spirometers. It may also be recorded from equipment used to measure static lung volumes and their subdivisions [42]. For slow VC, a maximum of four manoeuvres is a practical upper limit. It is preferable that VC manoeuvres be performed before FVC manoeuvres because of the potential for muscular fatigue and volume history effects, where, after maximal inspiratory efforts, some patients with severe airways obstruction return to a falsely high level of FRC or RV, due to gas trapping or stress relaxation [3]. The VC manoeuvre may be considered either as an IVC, where the subject inhales completely from a position of full expiration, or as an EVC, where the subject exhales completely from a position of full inspiration. Figure 11 shows the recording of IVC and figure 12 shows an EVC recording. Important differences between inspiratory (*i.e.* IVC) and expiratory (*i.e.* EVC) manoeuvres may be observed in patients with airways obstruction [43, 44].

The test is begun by instructing the subject in the VC manoeuvre and demonstrating the appropriate technique. It is important that subjects understand they must completely fill and empty their lungs. The VC manoeuvre is performed with the subject using a mouthpiece and wearing a nose clip. The

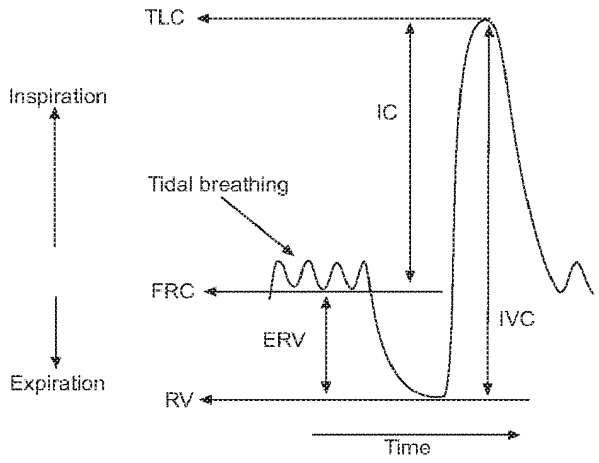

FIGURE 11. Tracing of tidal breathing followed by an expiratory manoeuvre to residual volume (RV), followed by a full inspiration to total lung capacity (TLC) to record inspiratory vital capacity (IVC) and inspiratory capacity (IC). FRC: functional residual capacity; ERV: expiratory reserve volume.

manoeuvre is not forced; it is performed in a relaxed manner, except near end-inspiration and end-expiration. The subject exhales completely to RV, then inhales to TLC, and finally exhales to RV again. The technician should encourage the subject to reach maximal inhaled and exhaled volumes with a relatively constant flow. The exhalation should not be unduly slow, as this can lead to underestimation of VC. Technicians should observe the subject carefully to ensure that his/her lips are sealed, nothing obstructs the mouthpiece, no leaks occur, and that TLC and RV are reached.

Alternatively, the subject inhales maximally, inserts the mouthpiece just past his/her front teeth, seals his/her lips around the mouthpiece, and blows slowly and evenly until there is no volume change (<0.025 L) for a 1-s period (see *End of test criteria* section). Patients with neuromuscular disease may need assistance in maintaining a tight seal at the mouth. The technician must observe the subject's inhalation to ensure

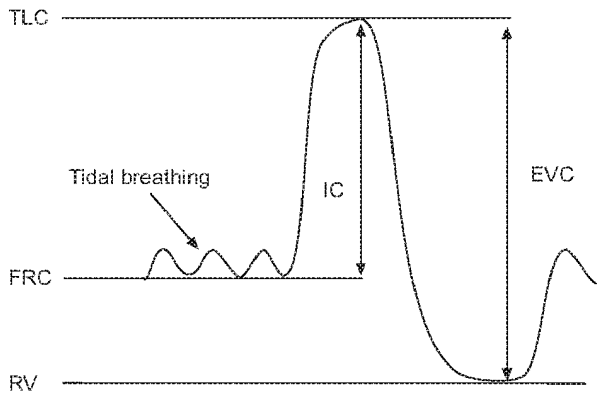

FIGURE 12. Tracing of tidal breathing followed by an inspiratory manoeuvre to total lung capacity (TLC) to record inspiratory capacity (IC), followed by a full expiration to residual volume (RV) to record expiratory reserve volume (EVC). FRC: functional residual capacity.

that it is complete, and that air is not exhaled while the mouthpiece is being inserted. The technician should assure that the expiratory manoeuvre is not forced. In healthy subjects, adequate maximal inspiratory and expiratory levels are achieved within 5–6 s.

IC

Subjects should be tested in the seated position wearing a nose clip with no air leaks between the mouth and the mouthpiece. Subjects should be relaxed (shoulders down and relaxed) and asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least three tidal manoeuvres). They are then urged to take a deep breath to TLC with no hesitation. Figure 12 shows a tracing from the recording of IC.

Use of a nose clip

The use of a nose clip is encouraged in VC measurements, since some people breathe through the nose when performing a slow VC manoeuvre. A nose clip must be used when performing inspiratory manoeuvres such as the IVC or IC.

Within-manoeuvre evaluation

These are the same as for FVC EOT criteria as described previously. There must be no leak at the mouth, no hesitation during the manoeuvre, and no obstruction of the mouthpiece (see *Additional criteria* section). The IC may be underestimated if the inspiratory manoeuvre is too slow due to poor effort or hesitation, or if there is premature closure of the glottis.

Between-manoeuvre evaluation

As with spirometry, a minimum of three acceptable VC manoeuvres must be obtained. If the difference in VC between the largest and next largest manoeuvre is >0.150 L, additional trials should be undertaken. Meeting repeatability criteria may require that up to, but usually no more than, four manoeuvres are performed, with a rest period of $\geq$1 min between the manoeuvres. Large variability in this test is often due to incomplete inhalations. Volume–time curves from the best two VC manoeuvres must be retained. For the IC, at least three acceptable manoeuvres should be performed. The mean coefficient of variation for IC in chronic airflow obstruction has been found to be 5 $\pm$3% [39].

Test result selection

For VC, the largest value from at least three acceptable manoeuvres should be reported. For IC, the average of at least three manoeuvres should be reported.

PEAK EXPIRATORY FLOW

Studies on the measurement of PEF are ongoing. Recent evidence has suggested that the previously applied standards may allow incorrect measurements to be made [45], and it is possible that more stringent requirements may be required. A further statement will be made when the position on the clinical significance of this is clear. However, since PEF measurements are part of asthma-management programmes, the previous recommendations [3, 46] are reiterated here.

Other instantaneous flow measurements (*e.g.* $FEF_{50\%}$, $FEF_{75\%}$) are not proven to be superior to conventional spirometric indices in a clinical setting, and, therefore, are not considered further.

Definition

PEF is the highest flow achieved from a maximum forced expiratory manoeuvre started without hesitation from a position of maximal lung inflation [46]. When it is obtained from flow–volume curve data, it is expressed at BTPS in $L \cdot s^{-1}$. The defining characteristics of the flow–time curve, in relation to PEF, are the time taken for flow to rise from 10% of PEF to 90% of PEF, *i.e.* the rise time (RT), and the duration that flow is >90% of PEF, called the dwell time (DT). When PEF is obtained with portable monitoring instruments, it is expressed in $L \cdot min^{-1}$.

Equipment

Ideally, PEF should be recorded by an instrument that primarily records flow. Measuring PEF requires an instrument that has a flat frequency response ($\pm$5%) up to 15 Hz [46]. Although there is evidence of significant frequency content in PEF up to 20 Hz [47], it is recommended, at this stage, that manufacturers achieve a goal of recording fidelity up to 15 Hz. The PEF must be measured with an accuracy of $\pm$10% or $\pm$0.3 $L \cdot s^{-1}$ (20 $L \cdot min^{-1}$), whichever is the greater. Mean instrument resistance measured across the range of the instrument should be <2.5 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ (0.25 $kPa \cdot L^{-1} \cdot s^{-1}$; table 6). PEF is sensitive to the resistance of the meter; for example, a resistance of 0.25 $kPa \cdot L^{-1} \cdot s^{-1}$ decreases PEF by ~8% compared with PEF measured with a low-resistance pneumotachograph [48].

Intra-instrument repeatability must be <5% or 0.150 $L \cdot s^{-1}$ (10 $L \cdot min^{-1}$), whichever is the greater. Inter-device reproducibility must be <10% or 0.300 $L \cdot s^{-1}$ (20 $L \cdot min^{-1}$), whichever is the greater. Calculating PEF by differentiating volume–time data may introduce noise; hence, a parabolic-fitting algorithm may be used [2] as a smoothing procedure.

Equipment validation is covered in the *Test signals for PEF meter testing* section.

Test procedure

PEF is dependent on effort and lung volume, with subject cooperation being essential. PEF must be achieved as rapidly as possible and at as high a lung volume as possible, in order to obtain the maximum value [49]. The subject must be encouraged to blow as vigorously as possible. The neck should be in a neutral position, not flexed or extended, and the subject must not cough. A nose clip is not necessary.

After the point of full lung inflation, the subject must deliver the blow without any delay. Hesitating for as little as 2 s or flexing the neck allows the tracheal visco-elastic properties to relax and PEF to drop by as much as 10% [50]. Tonguing, spitting or coughing at the start of the blow may falsely raise the recorded PEF in some devices.

In the laboratory, the subject must perform a minimum of three PEF manoeuvres. When PEF is a self-administered recording, it is important that the subject has been adequately taught how to perform the test, when to perform it and what action to take depending on the resulting value obtained. Regular checks of the patient's PEF technique and meter are an important part of the follow-up.

Within-manoeuvre evaluation

The subject must be observed to ensure a good seal at the mouth, no hesitation occurred, and there was no abnormal start to the manoeuvre.

Between-manoeuvre evaluation

The PEF values and their order must be recorded so that manoeuvre-induced bronchospasm can be detected. If the largest two out of three acceptable blows are not reproducible within 0.67 $L \cdot s^{-1}$ (40 $L \cdot min^{-1}$), up to two additional blows can be performed. Ninety-five per cent of untrained healthy subjects and patients can reproduce PEF to within 0.67 $L \cdot s^{-1}$ (40 $L \cdot min^{-1}$), and 90% to within 0.5 $L \cdot s^{-1}$ (30 $L \cdot min^{-1}$) [48]. If satisfactory repeatability has not been in achieved in five attempts, more are not likely to be helpful [51].

Test result selection

The largest value from at least three acceptable blows is recorded.

MAXIMUM VOLUNTARY VENTILATION

This test has been largely superseded by FEV1, which was defined as the index from a single maximum forced expiratory manoeuvre that best correlated with maximum voluntary ventilation (MVV). If FEV1 is available, then MVV has little additional contribution to make in a clinical setting. However, it may be useful in those conditions where ventilatory capacity may be impaired by mechanisms that are different from those affecting FEV1 [26].

Definition

The MVV is the maximum volume of air a subject can breathe over a specified period of time (12 s for normal subjects). It is expressed in $L \cdot min^{-1}$ at BTPS.

Equipment

A spirometer used for measuring MVV must have an amplitude–frequency response that is flat (±10%) from zero to ⩾4 Hz, at flows of up to 12 $L \cdot s^{-1}$, over the volume range. The time for exhaled volume integration or recording must be no less than 12 s and no more than 15 s [52]. The indicated time must be accurate to within ±3%. The MVV must be measured with an accuracy of ±10% of reading or ±15 $L \cdot min^{-1}$, whichever is greater.

The evaluation of equipment is covered in the *Test signals for MVV testing* section.

Test procedure

The technician should provide proper instructions and demonstrate the manoeuvre prior to the start of testing. The subject should be tested in the sitting position wearing a nose clip. After the subject makes an airtight seal around the mouthpiece, at least three resting tidal breaths should be obtained, followed by breathing as rapidly and deeply as possible. The tongue and teeth must be positioned so as to not obstruct airflow. The technician should enthusiastically coach the subject throughout the manoeuvre, and may need to suggest faster or slower breathing to achieve an ideal rate of 90–110 $breaths \cdot min^{-1}$ [53, 54], although subjects with disease may not always achieve this rate. The technician will need to carefully observe the subject with occasional glances at the tracing to help the subject to obtain an acceptable manoeuvre. An acceptable manoeuvre should be performed with maximal effort without evidence of leakage, hesitation or measurement artefact. The subject is instructed to breathe as deeply and rapidly as possible and the tidal volume (V_T) during the manoeuvre should be greater than the subject's resting V_T.

The test interval (*e.g.* 12 s) should be reported. A rest between manoeuvres will improve subsequent efforts.

The MVV should be calculated from the sum of all individual exhalations, multiplied by the appropriate BTPS correction factor during the best 12 s of the manoeuvre. From a technical standpoint, changes in respiratory rate or V_T during the manoeuvre will influence test results.

Within-manoeuvre evaluation

In normal subjects, the goal for an acceptable MVV should be a V_T that is ~50% of the VC, with a breathing frequency that is ~90 $breaths \cdot min^{-1}$ [54]. It is unlikely that an acceptable manoeuvre will be obtained when the breathing frequency is <65 $breaths \cdot min^{-1}$ [54]. However, since there are little data on MVV acceptability criteria, no specific breathing frequency or volume is required. The emphasis should be on maximal effort with a goal of 90 $breaths \cdot min^{-1}$ and a volume representing ~50% of the VC. V_T during the manoeuvre is probably not as important as breathing frequency, since patients tend to breathe on the portion of the expiratory curve where air is best moved at a given frequency.

Between-manoeuvre evaluation

The subject should perform a minimum of two acceptable manoeuvres. There are no clinical studies addressing repeatability; however, additional trials should be considered when the variability between acceptable manoeuvres exceeds 20%.

Test result selection

The highest acceptable MVV ($L \cdot min^{-1}$ BTPS) and MVV rate ($breaths \cdot min^{-1}$) should be reported. An MVV/(40 × FEV1) <0.80 indicates that the MVV is low relative to the FEV1, and suggests disease or poor effort. Volume *versus* time tracings from at least two acceptable manoeuvres should be retained and available for inspection.

TECHNICAL CONSIDERATIONS

Minimal recommendations for spirometry systems

Accurate results require accurate equipment. Spirometer equipment recommendations apply to all spirometers and are minimal requirements. In some circumstances, it may be appropriate to exceed these requirements (*i.e.* in some research/surveillance applications). Instrumentation recommendations should be followed to provide accurate spirometric data and information that is comparable from laboratory to laboratory and from one time period to another [1]. The accuracy of a spirometry system depends on characteristics of the entire system, from the volume or flow transducer and the use of an in-line filter, to the recorder, display or processor. Changes in any aspect of the equipment or errors at any step in the process can affect the accuracy of the results. For example, if the BTPS correction factor is wrong, an accurately measured FVC will be incorrectly reported.

Spirometers and PEF meters are not required to measure all of the indices in table 6, but must meet the recommendations for those that are measured. Accuracy and repeatability recommendations apply over the entire volume range of the instrument.

BTPS correction

All spirometry values should be reported at BTPS by any method (measuring temperature and barometric pressure) proven effective by the manufacturer. For volume-type spirometers, the temperature inside the spirometer should be measured for each breathing manoeuvre. Regardless of the BTPS correction technique used, the ambient temperature must always be recorded with an accuracy of ±1℃. In situations where the ambient air temperature is changing rapidly (>3℃ in <30 min), continuous temperature corrections may be necessary. Spirometer users should be aware of potential problems with testing performed at lower ambient temperatures: 17℃ is the lower limit [55–63] for ambient temperature, unless a manufacturer states that their spirometer will operate accurately at lower ambient temperatures. If barometric pressure is not used in calculating the BTPS correction factor, the range of barometric pressures over which the BTPS correction factor is valid must be published by the manufacturer.

Comments

The rationale for this recommendation is based, in part, on the problems with finite cooling times of gases in volume-type spirometers [55–57] and the problems of estimating BTPS correction factors for flow devices [58–60]. When a subject performs an FVC manoeuvre, the air leaving the lungs is ~33–35℃ [61, 62] and saturated with water vapour. If the expired gas is assumed to be at BTPS, an error of ~1% will result. Most volume-type spirometers assume instantaneous cooling of the air as it enters the spirometer. This is not always the case, and FEV_t can be incorrectly reported because of it. For capillary and screen pneumotachometers, the signal depends on gas viscosity, which increases with increasing temperature. Therefore, for pneumotachometers, a different correction factor is needed for recording patients as compared with recording from the calibrating syringe. Also, correction factors will be different for inspiratory and expiratory manoeuvres. It is usually assumed that expired gas does not cool as it passes through the flow sensor. This may not be the case, particularly with unheated flow sensors [58, 59]. The error will increase if the flow sensor is located further from the mouth and more cooling occurs, as is the case when a filter is placed in front of the flow sensor. Water condensation within or on the surfaces of a flow sensor may alter its calibration.

Depending on environmental temperature, the BTPS correction factor may be as large as 10%. The method used to calculate or estimate the BTPS factor can potentially introduce significant errors; examples and a fuller explanation can be found elsewhere [3, 4].

Changes in spirometer temperature can be a source of variability. Spirometer temperature should be measured and not assumed to be constant, even over the course of one testing

TABLE 6 Range and accuracy recommendations specified for forced expiratory manoeuvres

Test	Range/accuracy (BTPS)	Flow range $L \cdot s^{-1}$	Time s	Resistance and back pressure	Test signal
VC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0–14	30		3-L Calibration syringe
FVC	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0–14	15	<1.5 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ (0.15 $kPa \cdot L^{-1} \cdot s^{-1}$)	24 ATS waveforms, 3-L Cal Syringe
FEV_1	0.5–8 L, ±3% of reading or ±0.050 L, whichever is greater	0–14	1	<1.5 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ (0.15 $kPa \cdot L^{-1} \cdot s^{-1}$)	24 ATS waveforms
Time zero	The time point from which all FEV: measurements are taken			Back extrapolation	
PEF	Accuracy: ±10% of reading or ±0.30 $L \cdot s^{-1}$ (20 $L \cdot min^{-1}$), whichever is greater; repeatability: ±5% of reading or ±0.15 $L \cdot s^{-1}$ (10 $L \cdot min^{-1}$), whichever is greater	0–14		Mean resistance at 200, 400, 600 $L \cdot min^{-1}$ (3.3, 6.7, 10 $L \cdot s^{-1}$) must be <2.5 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ (0.25 $kPa \cdot L^{-1} \cdot s^{-1}$)	26 ATS flow waveforms
Instantaneous flows (except PEF)	Accuracy: ±5% of reading or ±0.200 $L \cdot s^{-1}$, whichever is greater	0–14		<1.5 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ (0.15 $kPa \cdot L^{-1} \cdot s^{-1}$)	Data from manufacturers
$FEF_{25-75\%}$	7.0 $L \cdot s^{-1}$, ±5% of reading or ±0.200 $L \cdot s^{-1}$, whichever is greater	±14	15	Same as FEV_1	24 ATS waveforms
MVV	250 $L \cdot min^{-1}$ at V_T of 2 L within ±10% of reading or ±15 $L \cdot min^{-1}$, whichever is greater	±14 (±3%)	12–15	<1.5 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ (0.15 $kPa \cdot L^{-1} \cdot s^{-1}$)	Sine wave pump

BTPS: body temperature and ambient pressure saturated with water vapour; VC: vital capacity; FVC: forced vital capacity; ATS: American Thoracic Society; FEV_1: forced expiratory volume in one second; FEV_t: forced expiratory volume in t seconds; PEF: peak expiratory flow; $FEF_{25-75\%}$: mean forced expiratory flow between 25% and 75% of FVC; MVV: maximum voluntary ventilation; V_T: tidal volume.

session. For volume spirometers, errors up to 6% in FEV1 and FVC can occur if ambient temperature is used instead of internal spirometer temperature [64]. For volume spirometers, the temperature inside the spirometer should be measured for each breathing manoeuvre.

Test signals for spirometer testing

The diversity of FVC manoeuvres encountered in clinical practice is currently best simulated by the 24 standard volume–time waveforms developed by the ATS [3] and HANKINSON and GARDNER [65]. These waveforms can be used to drive a computer-controlled mechanical syringe, or its equivalent, for testing actual hardware and software [66, 67], or, when put in a digital form, they can evaluate only the software. Computer-controlled mechanical syringes (*i.e.* pump systems) used for validation should be accurate within ±50 mL, which is 0.5% of their full range up to 10 L for FVC and FEV1. Pump systems may have accuracy values better than this for many profiles, but reproduce less accurately those test profiles with short DTs and RTs to peak flow [68, 69]. The ATS spirometry statement [3] shows the measured values for each of the 24 standard waveforms. On request, the ATS can provide these waveforms in an electronic format. Appropriate corrections for using gas at the ambient temperature and humidity instead of BTPS may need to be made for some mechanical syringe–spirometer combinations.

Method

A production spirometer is connected to the pump system for testing, orientated as it would be to test human subjects. Connecting tubing must be kept to the minimum (<0.300 L) and must not be distensible. If an in-line filter is required for testing human subjects, one must be included when the instrument is tested. Each of the 24 ATS waveforms is discharged into the spirometer five times under ambient conditions, and all of the readings are recorded.

BTPS conditions are simulated by discharging waveforms 1–4 to the spirometer three times, using air heated to 37±1℃ and at >98% relative humidity. The time between each of the three tests should be <2 min.

Accuracy test

The average of the five tests under ambient conditions is compared with the standard value in the following way:

$$\text{Deviation} = \text{average} - \text{standard} \quad (1)$$

$$\text{Percentage deviation} = 100 \times (\text{average} - \text{standard})/\text{standard} \quad (2)$$

The accuracy validation limits for volumes, which include the waveform-generator inaccuracy, are ±3.5% of reading or ±0.100 L, whichever is greater. An accuracy error occurs if the deviation (for volumes <2.857 L) or percentage deviation (for volumes >2.857 L) exceed these limits. These limits include the allowable inaccuracy of the pump system.

Acceptable spirometer performance is defined as fewer than three accuracy errors for either FVC or FEV1 across the 24 waveforms (<5% error rate).

The average FVC and FEV1 values of the three tests simulating BTPS conditions are compared with the standard values. The validation limits for these tests under BTPS conditions are ±4.5% or 0.200 L, whichever is the greater, and these limits include the allowable inaccuracy for the pump system.

Acceptable spirometer performance under BTPS conditions is defined as the accuracy requirement being met for all of the four profiles used.

Repeatability test

The FEV1 and FVC data from the accuracy test are used to derive the span of the five recordings:

$$\text{Span} = \text{maximum} - \text{minimum} \quad (3)$$

$$\text{Percentage span} = 100 \times \text{span}/\text{average} \quad (4)$$

The repeatability validation limits for the volume measured at ambient conditions are ±3.5% or ±0.100 L, whichever is the greater, and, for BTPS conditions, ±4.5% or ±0.200 L, whichever is the greater. A repeatability error occurs if the span (for volumes <2.857 L at ambient or 4.444 L at BTPS) or percentage span (for volumes above this) exceeds these limits.

Acceptable spirometer performance for repeatability under ambient conditions is defined as fewer than three accuracy errors for either FVC or FEV1 across the 24 profiles (<5% error rate). For BTPS conditions, the acceptable spirometer performance for repeatability is defined as the accuracy requirement being met for all of the four profiles.

Test signals for PEF meter testing

The 26 flow–time ATS waveforms were chosen to represent a range of PEF profiles suitable for delivery by mechanical syringe or pump systems to test PEF meters [3]. The range of profiles and method of delivery may need to be revised, as research on PEF measurement continues [45]. The mechanical syringe or suitable pump system used to validate PEF measuring equipment must have an accuracy of ±2% in delivering PEF. Pump systems may have difficulty meeting this accuracy standard for profiles more demanding than the set of 26 [68, 69]. Recent evidence suggests that the frequency content in the first second of the blow that contributes to PEF is higher [47] than previously determined [70, 71]. The 26 waveforms may not cover the range of RT and DT found in ~25% of the client population [72], and, hence, more demanding test profiles may be required in future [45].

Method

Two randomly chosen production models of the flow meters should each have the 26 waveforms delivered to them five times under ambient conditions and the readings recorded. Any waveforms with a PEF outside the meter's stated operational range would not be included in the testing sequence. Appropriate correction factors for testing under ambient conditions should be applied as recommended by the manufacturer.

Accuracy test

The average reading for each of the two meters is compared with the standard, as for volumes.

The accuracy validation limits are ±12% or ±25 L·min^{-1}, whichever is the larger, and these limits include the 2% inaccuracy limit for the waveform generator. An accuracy error

for a given meter and given waveform occurs if the deviation and percentage deviation exceed these limits.

Acceptable performance is defined as fewer than three accuracy errors out of the total of 52 tests (26 waveforms, two meters).

Repeatability test

Flow waveforms 1, 4, 8 and 25 are discharged three times to each of 10 production meters. The repeatability validation limits are ±6% or ±15 L·min^{-1}, whichever is the greater, and these limits include 1% for waveform-generator variability. A repeatability error occurs if the span and percentage span exceed these limits.

Acceptable performance is defined as six or fewer errors in the 120 tests (*i.e.* maximum error rate of 5%).

Test signals for MVV testing

A spirometry system used to measure MVV should be tested under ambient conditions with a pump producing a sinusoidal waveform, with stroke volumes up to 2 L using the four patterns of delivery previously specified [3]. Testing at BTPS is not required, and each pattern is tested twice. The accuracy validation limits of the spirometer used for measuring MVV with flows up to 250 L·min^{-1} are ±10.5% of reading or ±20 L·min^{-1}, whichever is greater. The pressure at the mouthpiece must not exceed ±10 cmH_2O (1 kPa) at any point during MVV testing. These requirements apply to volume spirometers throughout their volume range.

Acceptable performance is defined as no errors in the eight tests (four patterns, twice).

ABBREVIATIONS

Table 7 contains a list of abbreviations and their meanings, which will be used in this series of Task Force reports.

TABLE 7 List of abbreviations and meanings

ATPD	Ambient temperature, ambient pressure, and dry
ATPS	Ambient temperature and pressure saturated with water vapour
BTPS	Body temperature (*i.e.* 37°C), ambient pressure, saturated with water vapour
C	Centigrade
CFC	Chlorofluorocarbons
cm	Centimetres
COHb	Carboxyhaemoglobin
$D_{L,CO}$	Diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor
$D_{L,CO}/V_A$	Diffusing capacity for carbon monoxide per unit of alveolar volume, also known as *K*CO
D_M	Membrane-diffusing capacity
DT	Dwell time of flow >90% of PEF
EFL	Expiratory flow limitation
ERV	Expiratory reserve volume
EV	Back extrapolated volume
EVC	Expiratory vital capacity
$F_{A,X}$	Fraction of gas X in the alveolar gas
$F_{A,X,t}$	Alveolar fraction of gas X at time t
$FEF_{25-75\%}$	Mean forced expiratory flow between 25% and 75% of FVC
$FEF_{X\%}$	Instantaneous forced expiratory flow when X% of the FVC has been expired
FEV_1	Forced expiratory volume in one second
FEV_t	Forced expiratory volume in t seconds
$F_{E,X}$	Fraction of expired gas X
$FIF_{X\%}$	Instantaneous forced inspiratory flow at the point where X% of the FVC has been inspired
$F_{I,X}$	Fraction of inspired gas X
FIVC	Forced inspiratory vital capacity
FRC	Functional residual capacity
FVC	Forced vital capacity
H_2O	Water
Hb	Haemoglobin
Hg	Mercury
Hz	Hertz; cycles per second
IC	Inspiratory capacity
IVC	Inspiratory vital capacity
KCO	Transfer coefficient of the lung (*i.e.* $D_{L,CO}/V_A$)
kg	Kilograms
kPa	Kilopascals
L	Litres
L·min^{-1}	Litres per minute
L·s^{-1}	Litres per second
lb	Pounds weight
$MEF_{X\%}$	Maximal instantaneous forced expiratory flow where X% of the FVC remains to be expired
MFVL	Maximum flow–volume loop
mg	Milligrams
MIF	Maximal inspiratory flow
mL	Millilitres
mm	Millimetres
MMEF	Maximum mid-expiratory flow
ms	Milliseconds
MVV	Maximum voluntary ventilation
P_{A,O_2}	Alveolar oxygen partial pressure
PB	Barometric pressure
PEF	Peak expiratory flow
P_{H_2O}	Water vapour partial pressure
P_{I,O_2}	Inspired oxygen partial pressure
θ (theta)	Specific uptake of CO by the blood
RT	Rise time from 10% to 90% of PEF
RV	Residual volume
s	Seconds
STPD	Standard temperature (273 K, 0°C), pressure (101.3 kPa, 760 mmHg) and dry
TB	Tuberculosis
TGV (or V_{TG})	Thoracic gas volume
t_I	Time taken for inspiration
TLC	Total lung capacity
Tr	Tracer gas
t_{tot}	Total time of respiratory cycle
V_A	Alveolar volume
$V_{A,eff}$	Effective alveolar volume
VC	Vital capacity
V_c	Pulmonary capillary blood volume
V_D	Dead space volume
V_I	Inspired volume
V_S	Volume of the expired sample gas
µg	Micrograms

APPENDIX

Proposal for a standard data format for spirometry

This proposal would not preclude the use of other data formats, but would require that a spirometer should at least be able to output data in the required format. The advantage of a standard format is the ease of moving data into data repositories, such as quality control, healthcare and research databases. It should simplify and reduce the cost of data transfer when users change instrument models and manufacturers. Easier transfer of data into healthcare databases has the potential for improving the utility of lung function by making more complete data readily available to clinicians and healthcare researchers. In research and clinical settings, a standard data format should simplify and reduce the cost of transferring data into quality control software and could contribute to improved overall test quality. Finally, it is time for this change; pulmonary function is one of the last medical arenas without a standard data format.

Proposed format

The spirometry data file will consist of an American Standard Code for Information Interchange, comma-delineated file with variable length records. Comma-delineated text files are easily generated and are standard import formats for several database programs. Although some redundancies will exist, each record shall represent one curve and will be terminated with a carriage return and line feed. The ATS will distribute examples of this data format from their web site.

Table 8 shows a list of parameters that must be included in every record. If a parameter is unavailable, the space must remain blank (",,"). The flow–time data points must be provided with a sampling interval of 0.01 s (100 samples·s^{-1}) in mL·s^{-1}. If necessary, interpolation or other techniques must

TABLE 8 List of parameters#

ID (patient identification)
Patient name
Data type (SP followed by E=expiratory or I=inspiratory, followed by S=single or B=best curve)
Barometric pressure (mmHg)
Temperature (°C) used in BTPS calculation
Relative humidity (%)
FVC quality attribute (A, B, C, D or F)
FEV_1 quality attribute (A, B, C, D or F)
Effort attribute (A, B, C, D or F)
Interpretation code (see ATS interpretation scheme)
Deleted manoeuvre (Y or N)
Acceptable manoeuvre (Y or N)
Technician quality control code (A, B, C, D or F)
Computer quality code (A, B, C, D or F)
Plateau achieved (Y or N)
Review (N or R for "needs review" or "was reviewed")
Date of review (DD/MM/YYYY)
Reviewer initials
BTPS factor (x.xxx)
Spirometer manufacturer
Spirometer model
Spirometer serial number
Spirometer type
Testing facility name
City
State/region
Zip/post code
Country
E-mail
Phone number
Calibration date (DD/MM/YYYY)
Calibration time (HH:MM)
Calibration result (P or F for "passed" or "failed")
Date (DD/MM/YYYY)
Time (HH:MM)
Technician ID (technician identification code or initials)
Manoeuvre number
Age (integer years)
Height (cm)
Weight (kg)
Sex (M or F)
Race (2-character race code)
Date of birth (DD/MM/YYYY)
Reference values source (first author surname and date of publication, *e.g.* "Knudson 1983")
Reference values correction factor (x.xx, 1.00 for no correction)
Testing position (standing, sitting or supine)
Test type (pre-, post-, bronchodilator, methacholine concentration or dose)
FVC (mL)
Extrapolated volume (mL)
FEV_1 (mL)
FEV_6 (mL)
PEF (mL·s^{-1})
$FEF_{25-75\%}$ (mL·s^{-1})
VC (mL)
Forced expiratory time (s)
Time to PEF (ms)
Predicted FVC (mL)
Predicted FEV_1 (mL)
Predicted FEV_6 (mL)
Predicted FEV_1/FVC% (xxx.x%)
Predicted FEV_1/FEV_6% (xxx.x%)
Comments text
Original sampling interval (ms)
Blank 1 or $FEF_{25\%}$
Blank 2 or $FEF_{50\%}$
Blank 3 or $FEF_{75\%}$
Blank 4 or $FEF_{80\%}$
Blank 5
Blank 6
Blank 7
Blank 8
Blank 9
Blank 10
Number of data points
Flow data points (mL·s^{-1}, variable number contained in number of data points)
Carriage return
Line feed

#: All text type variables should be enclosed with double quotes (") to prevent confusion with control or data separator type characteristics.

be used to provide the 0.01-s sampling interval. The record length will vary, depending on the number of data points present in the flow–time portions of the record. The curve data must include ≥ 0.25 s of data points prior to the onset of the inspiratory or expiratory manoeuvre.

Volume–time curves may be calculated by adding the flow–time values ($mL \cdot s^{-1}$) and multiplying the sum by 0.01 s. To obtain the highest precision, the sum of the flow values should be calculated for each volume data point before multiplying by 0.01 s.

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REFERENCES

1 Renzetti AD Jr. Standardization of spirometry. *Am Rev Respir Dis* 1979; 119: 831–838.
2 American Thoracic Society. Standardization of spirometry: 1987 update. *Am Rev Respir Dis* 1987; 136: 1285–1298.
3 American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
4 Quanjer PH, ed. Standardized lung function testing. Report Working Party Standardization of Lung Function Tests. European Community for Coal and Steel. *Bull Eur Physiopathol Respir* 1983; 19: Suppl. 5, 1–95.
5 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volume and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* 1993; 6: Suppl. 16, 5–40.
6 Morgan KC. The assessment of ventilatory capacity (committee recommendations). *Chest* 1975; 67: 95–97.
7 Gardner RM, Crapo RO, Billings RG, Shigeoka JW, Hankinson JL. Spirometry: what paper speed? *Chest* 1983; 84: 161–165.
8 Gardner RM, Clausen JL, Crapo RO, *et al.* Quality assurance in pulmonary function laboratories. *Am Rev Respir Dis* 1986; 134: 626–627.
9 Morris AH, Kanner RE, Crapo RO, Gardner RM. Clinical pulmonary function testing: a manual of uniform laboratory procedures. 2nd Edn. Salt Lake City, UT, Intermountain Thoracic Society, 1984.
10 Townsend MC. The effects of leaks in spirometers on measurement of pulmonary function. *J Occup Med* 1984; 26: 835–841.
11 Association for the Advancement of Medical Instrumentation, Standard for spirometers (draft), October 1980. AAMI Suite 602, 1901 N. Ft. Myer Drive, Arlington, VA 22209–1699.
12 D'Angelo E, Prandi E, Milic-Emili J. Dependence of maximal flow-volume curves on time course of preceding inspiration. *J Appl Physiol* 1993; 75: 1155–1159.
13 Stoller JK, Basheda S, Laskowski D, Goormastic M, McCarthy K. Trial of standard *versus* modified expiration to achieve end-of-test spirometry criteria. *Am Rev Respir Dis* 1993; 148: 275–280.
14 Bucca CB, Carossa S, Colagrande P, *et al.* Effect of edentulism on spirometric tests. *Am J Respir Crit Care Med* 2001; 163: 1018–1020.
15 Eigen H, Bieler H, Grant D, *et al.* Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med* 2001; 163: 619–623.
16 Smith AA, Gaensler EA. Timing of forced expiratory volume in one second. *Am Rev Respir Dis* 1975; 112: 882–885.
17 Horvath EP Jr, ed. Manual of spirometry in occupational medicine. Division of Training and Manpower Development, National Institutes for Occupational Safety and Health. Cincinnati, NIOSH, 1981.
18 Hankinson JL, Gardner RM. Standard waveforms for spirometer testing. *Am Rev Respir Dis* 1982; 126: 362–364.
19 Aurora P, Stocks J, Oliver C, *et al.* Quality control for spirometry in preschoolchildren with and without lung disease. *Am J Crit Care Med* 2004; 169: 1152–1159.
20 Desmond KJ, Allen PD, Demizio DL, Kovesi T, Coates AL. Redefining end of test (EOT) criteria for pulmonary function testing in children. *Am J Respir Crit Care Med* 1997; 156: 542–545.
21 Hankinson JL, Bang KM. Acceptability and reproducibility criteria of the American Thoracic Society as observed in a sample of the general population. *Am Rev Respir Dis* 1991; 143: 516–521.
22 Ferris BG Jr, Speizer FE, Bishop Y, Prang G, Weener J. Spirometry for an epidemiologic study: deriving optimum summary statistics for each subject. *Bull Eur Physiopathol Respir* 1978; 14: 146–166.
23 Kanner RE, Schenker MB, Munoz A, Speizer FE. Spirometry in children: methodology for obtaining optimal results for clinical and epidemiological studies. *Am Rev Respir Dis* 1983; 127: 720–724.
24 Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardno LA, Crapo RO. FEV(6) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. *Am J Respir Crit Care Med* 2000; 162: 917–919.
25 Paoletti P, Pistelli G, Fazzi P, *et al.* Reference values for vital capacity and flow-volume curves from a general population study. *Bull Eur Physiopathol Respir* 1986; 22: 451–459.

26 Pellegrino R, Viegi G, Enright P, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005 (In press).
27 Coates AL, Allen PD, MacNeish CF, Ho SL, Lands LC. Effect of size and disease on expected deposition of drugs administered using jet nebulization in children with cystic fibrosis. *Chest* 2001; 119: 1123–1130.
28 Coates AL, Ho SL. Drug administration by jet nebulization. *Pediatr Pulmonol* 1998; 26: 412–423.
29 Newman SP, Clark AR, Talaee N, Clark SW. Pressurized aerosol deposition in the human lung with and without an "open" spacer device. *Thorax* 1989; 44: 706–710.
30 Tal A, Golan H, Grauer N, Aviram M, Albin D, Quastel MR. Deposition pattern of radiolabeled salbutamol inhaled from a meter-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996; 128: 479–484.
31 Newhouse MT. Asthma therapy with aerosols: are nebulizers obsolete? A continuing controversy. *J Pediatr* 1999; 135: 5–8.
32 Coates AL, MacNeish CF, Lands LC, Meisner D, Kelemen S, Vadas EB. A comparison of the availability of tobramycin for inhalation from vented *versus* unvented nebulizers. *Chest* 1998; 113: 951–956.
33 Devadason SG, Everard ML, Linto JM, LeSouëf PN. Comparison of drug delivery form conventional *versus* "Venturi" nebulizers. *Eur Respir J* 1997; 10: 2479–2483.
34 Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers. *Chest* 2002; 122: 510–516.
35 Wildhaber JH, Devadason SG, Hayden MJ, Elber E, Summers QA, LeSouëf PN. Aerosol delivery to wheezy infants: a comparison between a nebulizer and two small volume spacers. *Pediatr Pulmonol* 1997; 23: 212–216.
36 Guidelines for the measurement of respiratory function. Recommendations of the British Thoracic Society and the Association of Respiratory Technicians and Physiologists. *Respir Med* 1994; 88: 165–194.
37 Babb TG, Viggiano R, Hurley B, Staats B, Rodarte JR. Effect of mild-to-moderate airflow limitation on exercise capacity. *J Appl Physiol* 1991; 70: 223–230.
38 O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after cholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 542–549.
39 Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction. *Chest* 1998; 114: 1607–1612.
40 Pellegrino R, Brusasco V. Lung hyperinflation and flow limitation in chronic airway obstruction. *Eur Respir J* 1997; 10: 543–549.
41 Younes M, Kivinen G. Respiratory mechanics and breathing pattern during and following maximal exercise. *J Appl Physiol* 1984; 57: 1773–1782.
42 Wanger J, Clausen JL, Coates A, Pedersen OF. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; (In press).
43 Brusasco V, Pellegrino R, Rodarte JR. Vital capacities during acute and chronic bronchoconstriction: dependence on flow and volume histories. *Eur Respir J* 1997; 10: 1316–1320.
44 Hansen LM, Pedersen OF, Lyager S, Naerra N. [Differences in vital capacity due to the methods employed]. *Ugerkr Laeger* 1983; 145: 2752–2756.
45 Miller MR, Atkins P, Pedersen OF. Inadequate peak expiratory flow meter characteristics detected by a computerised explosive decompression device. *Thorax* 2003; 58: 411–416.
46 Quanjer PH, Lebowitz MD, Gregg I, Miller MR, Pedersen OF. Peak expiratory flow: conclusions and recommendations of the European Respiratory Society. *Eur Respir J* 1997; 10: Suppl. 24, 2s–8s.
47 Miller MR, Lloyd J, Bright P. Recording flow in the first second of a maximal forced expiratory manoeuvre: influence of frequency content. *Eur Respir J* 2002; 19: 530–533.
48 Pedersen OF, Rasmussen TR, Omland Ø, Sigsgaard T, Quanjer PH, Miller MR. Peak expiratory flow and the resistance of the mini-Wright peak flow meter. *Eur Respir J* 1996; 9: 828–833.
49 Pedersen OF, Pedersen TF, Miller MR. Gas compression in lungs decreases peak expiratory flow depending on resistance of peak flow meter. *J Appl Physiol* 1997; 83: 1517–1521.
50 Kano S, Burton DL, Lanteri CJ, Sly PD. Determination of peak expiratory flow. *Eur Respir J* 1993; 6: 1347–1352.
51 Ferris BG Jr, Speizer FE, Bishop Y, *et al.* Spirometry for an epidemiologic study: deriving optimum summary statistics for each subject. *Bull Eur Physiopathol Respir* 1978; 14: 145–166.
52 Federal Register, 38:4265, Feb. 12, 1973, Section of pulmonary function specifications. Washington, DC, United States Government Printing Office.
53 Bernstein L. The effect of the rate of breathing on maximum breathing capacity determined with a new spirometer. *Thorax* 1952; 7: 255–262.
54 Miller WF, Johnson RL Jr, Wu N. Relationships between maximal breathing capacity and timed expiratory capacities. *J Appl Physiol* 1959; 14: 510–516.
55 Hankinson JL, Viola JO. Dynamic BTPS correction factors for spirometric data. *J Appl Physiol* 1983; 44: 1354–1360.
56 Hankinson JL, Castellan RM, Kinsley KB, Keimig DG. Effects of spirometer temperature on FEV1 shift changes. *J Occup Med* 1986; 28: 1222–1225.
57 Pincock AC, Miller MR. The effect of temperature on recording spirograms. *Am Rev Respir Dis* 1983; 128: 894–898.
58 Hankinson JL, Viola JO, Petsonk EL, Ebeling TR. BTPS correction for ceramic flow sensors. *Chest* 1994; 105: 1481–1486.
59 Miller MR, Pincock AC. Linearity and temperature control of the Fleisch pneumotachograph. *J Appl Physiol* 1986; 60: 710–715.
60 Perks WH, Sopwith T, Brown D, Jones CH, Green M. Effects of temperature on Vitalograph spirometer readings. *Thorax* 1983; 38: 592–594.
61 Cole P. Recordings of respiratory air temperature. *J Laryngol* 1954; 68: 295–307.
62 Madan I, Bright P, Miller MR. Expired air temperature at the mouth during a maximal forced expiratory manoeuvre. *Eur Respir J* 1993; 6: 1556–1562.

63 Liese W, Warwick WJ, Cumming G. Water vapour pressure in expired air. *Respiration* 1974; 31: 252–261.
64 Johnson LR, Enright PL, Voelker HT, Tashkin DP. Volume spirometers need automated internal temperature sensors. *Am J Respir Crit Care Med* 1994; 150: 1575–1580.
65 Hankinson JL, Gardner RM. Standard waveforms for spirometer testing. *Am Rev Respir Dis* 1982; 126: 362–364.
66 Nelson SB, Gardner RM, Crapo RO, Jensen RL. Performance evaluation of contemporary spirometers. *Chest* 1990; 97: 288–297.
67 Gardner RM, Hankinson JL, West BJ. Evaluating commercially available spirometers. *Am Rev Respir Dis* 1986; 134: 626–627.
68 Hankinson JL, Reynolds JS, Das MK, Viola JO. Method to produce American Thoracic Society flow–time waveforms using a mechanical pump. *Eur Respir J* 1997; 10: 690–694.
69 Miller MR, Jones B, Xu Y, Pedersen OF, Quanjer PH. Peak expiratory flow profiles delivered by pump systems: limitations due to wave action. *Am J Respir Crit Care Med* 2000; 162: 1887–1896.
70 Peslin R, Jardin P, Bohadana A, Hannhart B. Contenu harmonique du signal de débit pendant l'expiration forcée chez l'homme normal [Harmonic content of the flow signal during forced expiration in normal man]. *Bull Eur Physiopath Respir* 1982; 18: 491–500.
71 McCall CB, Hyatt RE, Noble FW, Fry DL. Harmonic content of certain respiratory flow phenomena of normal individuals. *J Appl Physiol* 1957; 10: 215–218.
72 Miller MR, Pedersen OF, Quanjer PH. The rise and dwell time for peak expiratory flow in patients with and without airflow limitation. *Am J Respir Crit Care Med* 1998; 158: 23–27.

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Pharmacodynamics, pharmacokinetics and safety of revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies

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ABSTRACT

Background: Revefenacin (TD-4208) is a potent, lung-selective, long-acting muscarinic antagonist currently in development as a once-daily nebulized therapy for chronic obstructive pulmonary disease (COPD). We evaluated the pharmacodynamics (bronchodilator activity), pharmacokinetics (PK) and safety of single- and multiple-dose administrations of revefenacin in two clinical trials (Study 0059 and Study 0091) in patients with moderate to severe COPD.

Methods: In Study 0059, 32 patients were randomized to receive a single dose of revefenacin (350 or 700 μg), active control ipratropium (500 μg) or placebo inhalation solution administered via standard jet nebulizer in a double-blind, crossover fashion. In Study 0091, 59 patients were randomized to receive once-daily inhalations of revefenacin (22, 44, 88, 175, 350 or 700 μg) or placebo for 7 days in a double-blind, incomplete block, five-way crossover design. The primary efficacy endpoint was change from baseline in peak (0–6 h) forced expiratory volume in 1 s (FEV_1) in Study 0059, and trough FEV_1 after the final dose (Day 7) in Study 0091. In both studies, secondary endpoints included area under the FEV_1-time curve (FEV_1 AUC) values from time 12–24 h post dose and FEV_1 AUC values from time zero to 24 h post dose.

Results: Revefenacin demonstrated a rapid onset and sustained duration of bronchodilator action in both studies. In Study 0059, mean peak FEV_1 was significantly higher ($p < 0.001$) for revefenacin and ipratropium compared to placebo, with differences of 176.8 mL for 350 μg revefenacin, 162.2 mL for 700 μg revefenacin and 190.6 mL for ipratropium. In Study 0091, mean trough FEV_1 on Day 7 was significantly higher ($p < 0.006$) for all revefenacin doses compared to placebo, with differences ranging from 53.5 mL (22 μg dose) to 114.2 mL (175 μg dose). The results for the other spirometry endpoints were consistent with the primary endpoint for each study, demonstrating that the bronchodilator effect of revefenacin lasted more than 24 h following nebulized administration. Revefenacin was rapidly absorbed and extensively metabolized, followed by a slow apparent terminal elimination and minimal accumulation with repeated dosing. In both studies, adverse events were generally mild and occurred with similar frequencies in all groups, with no indication of significant systemic anti-muscarinic activity at any dose.

Conclusions: Following single or multiple nebulized-dose administration in patients with COPD, revefenacin demonstrates a rapid onset and sustained duration of bronchodilator effect over 24 h following once-daily administration, with a PK profile that is commensurate with low systemic exposure.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common and progressive condition characterized by airflow limitation that is not fully reversible and is associated with high morbidity, mortality and burden on society [1,2]. Conservative estimates anticipate that by the year 2030, COPD will be the third leading cause of global mortality, directly responsible for 7.8% of all deaths [2]. Globally, chronic respiratory diseases account for 6.3% of years lost due to disability, with COPD being the largest contributor, making up two-thirds of the global disability-adjusted life years [2].

Inhaled bronchodilator therapy is central to the management of stable COPD, most commonly using β_2-agonists and muscarinic antagonists, with long-acting bronchodilators considered to provide more convenient and effective symptom relief than short-acting bronchodilators [1,3,4]. Bronchodilators are generally administered by either dry powder or pressurized metered-dose inhalers, but these devices may not be suitable for all patients [1,5]. Some patients require or prefer to use a nebulizer because of limitations in physical or cognitive function and/or disease severity [6,7], and approximately 9% of COPD patients in the United States are treated using nebulizers for ongoing therapy [8]. In addition, clinicians often prescribe use of nebulizers in the acute setting and for exacerbations, as nebulized delivery is a practical method of drug delivery requiring minimal cognitive ability, hand-breath coordination or manual dexterity [9].

Revefenacin (TD-4208) is a new, potent long-acting muscarinic antagonist (LAMA) with functional lung selectivity and long duration of effect in pre-clinical models of bronchoconstriction [10,11], and is currently in development as a once-daily inhalation therapy administered via nebulizer for the treatment of COPD [9,12,13]. Here we report the results of two phase 2 studies (Study 0059 and Study 0091), the objectives of which were to evaluate the bronchodilator activity, pharmacokinetics (PK) and safety of single and multiple nebulized doses of revefenacin in patients with COPD in order to provide an initial assessment of efficacy and safety in the relevant patient population, and to inform dose selection for subsequent phase 2 and 3 clinical studies.

2. Methods

2.1. Study design and conduct

The two phase 2 studies were randomized, double-blind and placebo-controlled. The PK, pharmacodynamics, safety and tolerability of revefenacin were evaluated in patients with COPD, following either a single dose using a four-period complete crossover design (Study 0059; universal trial identifier: U1111-1120-8290 [14]) or multiple doses (revefenacin administered once daily for 7 days) using a five-period, incomplete block crossover design (Study 0091; national clinical trial identifier: 01704404 [15]).

Study 0059 was conducted at two centers (South Africa and New Zealand) between May 2011 and October 2011, and Study 0091 was conducted at three centers (United Kingdom, Northern Ireland and New Zealand) between December 2012 and August 2013.

The protocol of each study was approved by the appropriate ethical committees for each study site, and the studies were conducted in accordance with the principles of the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice [16] and the Code of Ethics of the World Medical Association Declaration of Helsinki [17], with all patients providing written informed consent.

2.2. Patients

Patients included in each study were men or women of non-childbearing potential, aged 40–75 years, with a current or former smoking history of more than 10 pack-years and able to demonstrate the following respiratory criteria at screening: a ratio of forced expiratory volume in 1 s (FEV_1)/forced vital capacity of <0.7 and FEV_1 of 35–80% of the predicted normal value after withholding short-acting bronchodilators for ≥6 h and long-acting bronchodilators for ≥24 h. In addition, patients in Study 0059 were required to demonstrate FEV_1 reversibility of ≥12% and ≥200 mL within 1 h of receiving 40 μg ipratropium bromide from a metered-dose inhaler, while patients in Study 0091 were required to demonstrate FEV_1 reversibility of ≥12% and ≥120 mL within 1 h of receiving 500 μg ipratropium bromide from a PARI LC Sprint® nebulizer (PARI, Midlothian, Virginia, US).

Patients were excluded if they had experienced a COPD exacerbation within 6 weeks of screening, if they had any change to their inhaled or oral corticosteroid, long-acting β_2 agonist or LAMA therapy within 4 weeks prior to screening or were receiving high-dose corticosteroid therapy (>1000 μg fluticasone propionate equivalent by inhalation or >5 mg (Study 0059) or >10 mg (Study 0091) oral prednisone daily). Patients were also excluded if they had a history of significant cerebrovascular disease, coronary artery disease or cardiac arrhythmias, hypersensitivity to the drug class or any other medical conditions or medication use that could put them at undue risk or potentially compromise the results of the studies. Concomitant treatment with other anti-muscarinic medications was prohibited throughout each study.

2.3. Treatments

In Study 0059, following the screening period (up to 21 days prior to first study treatment), patients were randomized according to a Williams square design to receive a single dose of each of four treatments (revefenacin 350 μg, revefenacin 700 μg and placebo in 10 mM citrate buffer in normal saline at pH 5.0, and ipratropium bromide inhalation solution 500 μg) administered via PARI LC® Plus jet nebulizer in a four-period crossover fashion separated by washout periods of 7–12 days. Patients were required to avoid using short-acting bronchodilators for ≥6 h and long-acting bronchodilators for ≥24 h before each treatment.

In Study 0091, following the screening period (up to 21 days prior to first study treatment), patients were randomized using an interactive web randomization system to receive one of five treatment sequences (five different treatment combinations, each ordered in 10 unique sequences), in which they received placebo and four out of six dose levels of revefenacin (22, 44, 88, 175, 350 and 700 μg) in 10 mM citrate buffer in normal saline at pH 5.0. Each treatment was administered once daily for 7 days via PARI LC Sprint nebulizer, and each treatment period was separated by 10–16 days of washout.

In Study 0059, solutions for nebulization were prepared by unblinded pharmacy staff who were not involved in any observation, data entry, monitoring or reporting other than drug accountability and dispensing records. All other study personnel, as well as the sponsor, site monitors and patients, were blinded to treatment allocation throughout the study.

In Study 0059, short-acting bronchodilators were prohibited from −12 h and tiotropium was prohibited from −72 h until 25 h post dose in each treatment period, and the following treatments were each prohibited from −24 h until 25 h post dose in each treatment period: ipratropium bromide, long-acting β-agonists,

inhaled corticosteroid/long-acting β-agonist combinations (e.g. Advair®, Symbicort®), oral leukotriene antagonists, other oral bronchodilators, theophylline, medications containing aspirin >100 mg/day, non-steroidal anti-inflammatory drugs and non-prescribed decongestants.

In Study 0091, revefenacin and placebo inhalation solutions were provided in pre-manufactured sterile, sealed glass vials. All study personnel, as well as the sponsor, site monitors and patients, were blinded to treatment allocation throughout the study. Short-acting bronchodilators (e.g. albuterol) were prohibited from −12 h before dosing on Day 1 and Day 7 in each treatment period; ipratropium bromide was prohibited from −24 h on Day 1 until Day 8 of each treatment period; LAMAs and once-daily long-acting bronchodilators were prohibited from Day −5 before each treatment period; medications containing twice-daily long-acting beta-agonists (e.g. Advair®, Symbicort®), oral leukotriene antagonists, other oral bronchodilators and theophylline were all prohibited from −48 h before each treatment period, and nasal decongestants were prohibited from −24 h before treatment on Day 1 of each treatment period.

2.4. Assessments and endpoints

2.4.1. Pharmacodynamic parameters

In Study 0059, FEV_1 measurements were obtained at screening, and in the four treatment periods at 0 (before dosing), 15, 30 and 45 min and 1, 2, 3, 4, 6, 8, 10, 11, 12, 14, 22, 23, 24 and 25 h post dose. The primary endpoint was mean change from baseline in peak FEV_1. Additional pharmacodynamic endpoints included trough FEV_1 and weighted mean area under the FEV_1-time curve (FEV_1 AUC) values from time 0–12 h post dose (FEV_1 AUC_{0-12h}) and 12–24 h post dose (FEV_1 AUC_{12-24h}).

In Study 0091, FEV_1 measurements were obtained at screening (before and after ipratropium bromide inhalation), and on Days 1 and 7 of each treatment period (at −45 min, approximately −15 min and 15 and 30 min and 1, 2, 3, 4, 6, 8, 10, 11, 12, 14, 22, 23, 24 and 25 h post dose). The primary endpoint was trough FEV_1 after the seventh dose (trough was the mean of the 23-h and 24-h post dose FEV_1 time points). Secondary endpoints included mean change from baseline in peak FEV_1 and the weighted mean FEV_1 AUC values.

2.4.2. PK parameters

In Study 0059, plasma samples were obtained for each treatment period at 0, 15, 30 and 45 min and 1, 2, 3, 4, 6, 8, 10, 12, 22 and 24 h post dose. Total urine collections were obtained during each treatment period from 0 to 12 and 12–24 h post dose. In Study 0091, blood samples were obtained before dosing, at 15 and 30 min and 1, 2, 3, 4 and 6 h after the first dose in each treatment period and at 0, 15 and 30 min and 1, 2, 3, 4, 6, 8, 12 and 24 h after the seventh dose of each treatment period.

Concentrations of revefenacin and its major plasma metabolite (THRX-195518) were quantified using validated liquid chromatography with tandem mass spectrometry. The lower limit of quantification for both revefenacin and its major metabolite was 0.005 ng/mL. Quality control accuracy (% relative error) and precision (% coefficient of variation) for the revefenacin and THRX-195518 PK assays did not exceed 5%.

Key PK parameters evaluated included maximum plasma concentration (C_{max}), the area under the plasma concentration-time curve from time 0 to last detectable time point (AUC_{0-t}), terminal elimination half-life ($t_{1/2}$) and, for Study 0059 only, renal clearance.

2.4.3. Safety and tolerability

For both studies, safety and tolerability were assessed based on adverse events (AEs), clinical laboratory findings (serum chemistry, hematology and urinalysis) on Day −1 of each treatment period (and additionally on Day 6 of each treatment period in Study 0091) and vital signs from before dosing until 24 h post dose on Day 1 of each study period (and additionally on Day 7 of each treatment period in Study 0091). In addition, electrocardiogram (ECG) recordings were obtained on Day 1 of each treatment period in Study 0091.

2.5. Statistical analysis

Sample size calculations for Study 0059 assumed that with enrollment of 32 patients, up to four might drop out, leaving 28 patients to provide 77% power to detect a 150-mL maximum increase from baseline FEV_1 based on a standard deviation (SD) of 200 mL to give a 5% level of significance. For Study 0091, with a sample size of 60 (10 patients assigned to each of six unique treatment combinations) and assuming up to 10 dropouts, 50 completers would provide at least 80% power to detect an increase of 120 mL in trough FEV_1 based on a within-subject SD of 115 mL. The study was not powered to assess dose-response.

In Study 0059, all lung function analyses were based on a modified per-protocol group, comprising all patients who contributed data up to the occurrence of any major deviations (non-compliance or use of prohibited medications). Pairwise comparisons of each pharmacodynamic endpoint were made between each dose of test treatment and placebo, using a gatekeeping approach to adjust for multiple comparisons (i.e. sequentially testing ipratropium bromide vs placebo, then revefenacin 700 μg, then revefenacin 350 μg and proceeding only if the preceding comparison was significant).

In Study 0091, the primary data set for pharmacodynamic analysis was the intent-to-treat (ITT) set, which included all patients who were randomized and received at least one dose of study drug. Data were also analyzed for the per-protocol set, which included all patients in the ITT analysis but excluded those who had used rescue medication during the 6-h or 24-h spirometry measurements and those with any missing FEV_1 measurements (patients were excluded for that day only). Analysis of covariance was used to compare treatment differences with placebo, adjusting for baseline. The primary endpoint was analyzed using a repeated measures mixed-effects model, incorporating study period and randomized treatment as factors and baseline FEV_1 as covariate. Least squares (LS) means and 95% confidence intervals (CIs) were calculated for the differences between each revefenacin dose and placebo, and statistical significance of the six pairwise comparisons vs placebo were evaluated using the Hochberg step-up adjustment for multiple comparisons.

In both studies, PK data were analyzed using summary statistics for all patients who provided PK data for at least one dose of revefenacin, and safety data were analyzed descriptively using SAS® Version 9.2 (Cary, North Carolina, US) or higher for all patients who received at least one dose of study drug (safety set) based on actual treatment received.

3. Results

3.1. Study subjects

Study 0059 enrolled 32 patients, each of whom received every study treatment, completed all follow-up assessments and were included in ITT and safety analyses (Fig. 1). Study 0091 enrolled 62 patients, each of whom was included in the safety set. Three patients discontinued from the study due to AEs and subsequent patient self-withdrawal and, therefore, the remaining 59 patients

who contributed pharmacodynamic data comprised the ITT set. Key baseline characteristics of patients included in each study are summarized in Table 1.

3.2. Pharmacodynamic parameters

3.2.1. Single-dose administration (study 0059)

Both revefenacin doses increased FEV_1 over the 25-h post-dose period (Fig. 2A). The primary endpoint, mean change in peak FEV_1 from baseline, demonstrated a significant increase with all active treatments relative to placebo (Fig. 3A). Treatment differences from placebo were significant for each revefenacin dose and ipratropium (all p values ≤ 0.001); the LS mean (95% CI) differences ranged from 162.2 (103.2, 221.1) mL for 700 μg revefenacin to 190.6 (131.7, 249.5) mL for 500 μg ipratropium (Table 2).

The secondary efficacy endpoint, change in trough FEV_1 from baseline, demonstrated significant benefit with both revefenacin doses relative to placebo (Fig. 3B); the LS mean (95% CI) treatment difference was 102.8 (54.1, 151.5) mL for the 350 μg dose and 136.6 (87.8, 185.3) mL for the 700 μg dose (both p values ≤ 0.001; Table 2). Trough FEV_1 was similar for ipratropium vs placebo.

Similar to ipratropium, the onset of bronchodilation with revefenacin was within 45 min of dosing and its peak FEV_1 effect was achieved by 2–3 h post dose (Fig. 2A). The sustained efficacy of revefenacin was demonstrated by evaluation of weighted mean FEV_1 AUC_{0-12h} and FEV_1 AUC_{12-24h} values on Day 1; the ratio of mean FEV_1 AUC values (FEV_1 $AUC_{12-24\ h}$/FEV_1 AUC_{0-12h}) was 0.969 and 0.989 for the 350 and 700 μg revenacin dose groups, respectively, indicating that the efficacy of revefenacin at each dose level was comparable between early and late inter-dose intervals.

3.2.2. Multiple-dose administration (study 0091)

On Day 7, the 25 h FEV_1 serial spirometry profile demonstrated a sustained duration of effect for all revefenacin doses (Fig. 2B). The FEV_1 was greater for all revefenacin doses relative to placebo at all time points post dose. The primary endpoint, change from baseline in trough FEV_1 24 h after the seventh dose, demonstrated significant benefit with all revefenacin doses relative to placebo (Fig. 4A) (all p values ≤ 0.006). There was a dose response effect on trough FEV_1 with revefenacin doses from 22 to 175 μg, with no further augmentation of bronchodilator effect with increases above the 175 μg dose. The LS mean (95% CI) treatment difference from placebo ranged from 53.5 (16.5, 90.5) mL for the 22 μg dose to 114.2 (75.7, 152.6) mL for the 175 μg dose (Table 3).

The secondary efficacy endpoint, change from baseline in peak FEV_1 after the first dose, also demonstrated significant benefit with all revefenacin doses relative to placebo (Fig. 4B). The peak FEV_1 changes showed dose dependency, with the 22 μg and 44 μg doses having LS mean (95% CI) treatment differences compared to placebo of 67.1 (34.1, 100.0) mL and 62.7 (28.9, 96.6) mL, respectively, while all higher doses caused mean changes of approximately 100 mL or greater, e.g., 142.8 (110.0, 175.7) mL was observed for the 350 μg dose (Table 3).

Table 1
Baseline characteristics (ITT population of each study).

Characteristic	Study 0059 ($N = 32$)	Study 0091 ($N = 59$)
Age, years		
Mean (range)	62.0 (46–74)	63.9 (45–75)
Sex, n (%)		
Males	22 (68.8)	33 (55.9)
Race, n (%)		
White	28 (87.5)	59 (100)
Other	4 (12.5)	0
BMI, kg/m^2		
Mean (SD)	27.72 (8.0)	28.8 (5.92)
Spirometry, mean (SD)		
FEV_1, % of predicted normal[a]	50.5 (13.7)	47.2 (12.4)
FEV_1, L[b]	1.9 (0.5)	1.6 (0.5)
FEV_1/FVC, %[b]	53.5 (10.8)	51.8 (9.8)
FEV_1, % change[b]	23.7 (8.7)	21.1 (14.3)

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ITT, intent to treat; SD, standard deviation.
[a] Prior to bronchodilators.
[b] Post bronchodilators.

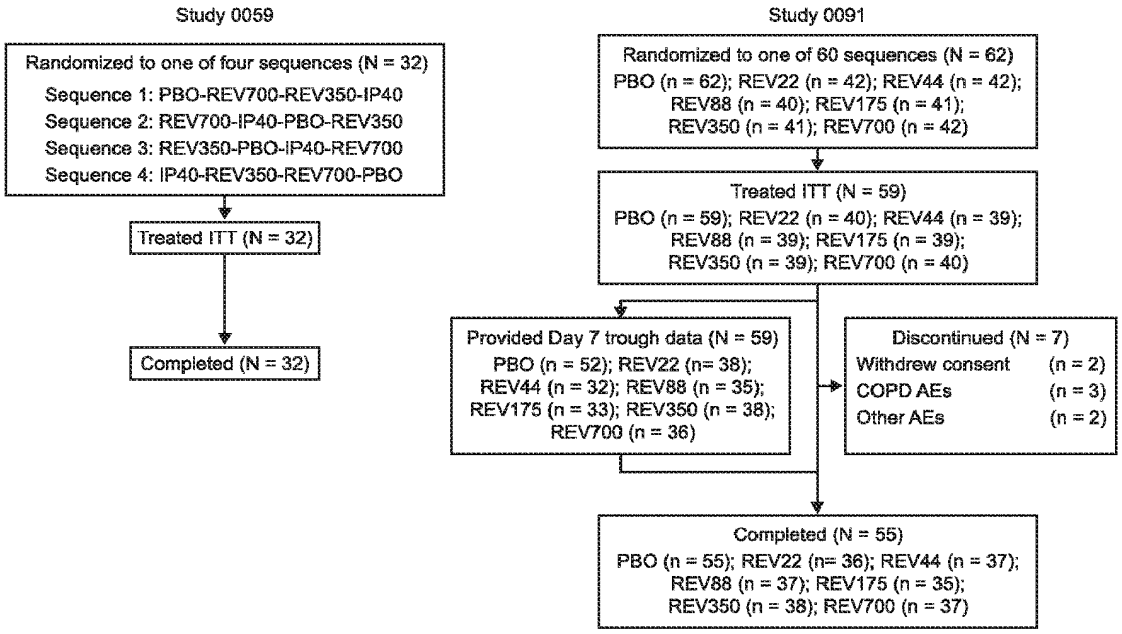

Fig. 1. Patient flow. AE, adverse event; COPD, chronic obstructive pulmonary disease; IP40, ipratropium 40 μg; ITT, intent to treat; REV(22, 44, 88, 175, 350 or 700), revefenacin (22, 44, 88, 175, 350 or 700) μg; PBO, placebo.

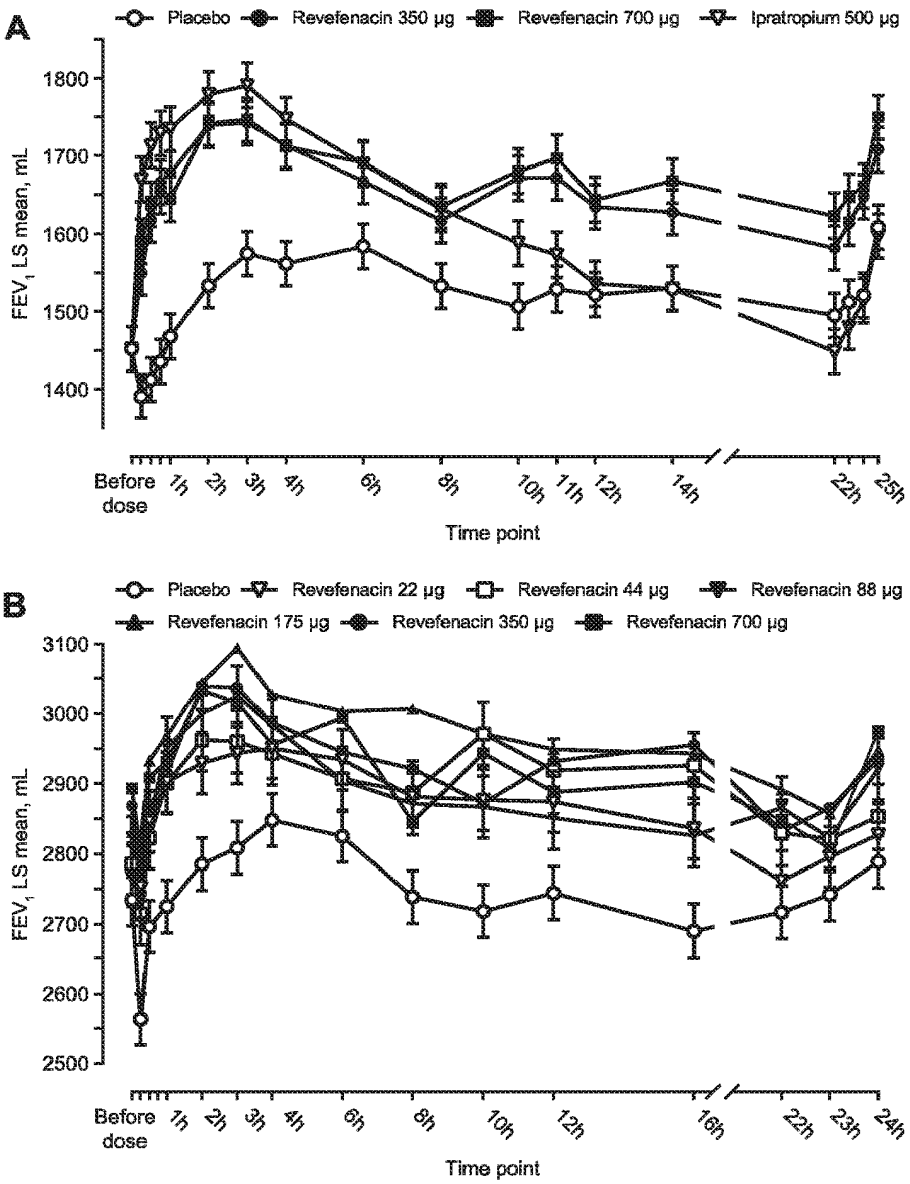

Fig. 2. Change in FEV_1 over time. Change in FEV_1 LS mean (SEM): A. after single-dose inhalations of revefenacin 350 or 700 µg, ipratropium 500 µg or placebo (Study 0059) (MPP group) and B. after the final dose of revefenacin 22, 44, 88, 175, 350 or 700 µg or placebo on Day 7 in Study 0091 (ITT population).
FEV_1, forced expiratory volume in 1 s; h, hour; ITT, intent to treat; LS, least squares; MPP, modified per protocol; SEM, standard error of the mean.

The Day 7 25-h FEV_1 serial spirometry profile for revefenacin demonstrated rapid onset of effect (treatment response evident within the first hour post dose) (Fig. 2B). The prolonged efficacy of revefenacin was also demonstrated by evaluation of FEV_1 AUC_{12-24h} and FEV_1 AUC_{0-12h} values on Day 7; the ratio of FEV_1 $AUC_{12-24\ h}$/FEV_1 AUC_{0-12h} for all dose groups was ≥0.95 (Table 3), indicating that the bronchodilatory effect of revefenacin at each dose level was comparable between early and late inter-dose intervals.

The proportion of patients achieving at least 100-mL increases in trough FEV_1 on Day 7 ranged from 33.3% with revefenacin 44 µg to 64.1% with revefenacin 350 µg, compared with 18.6% of placebo-treated patients (Table 3).

3.3. *Systemic pharmacokinetics*

Data from both studies indicated that revefenacin was rapidly absorbed into the systemic compartment and demonstrated bi-exponential elimination (rapidly declining plasma concentrations followed by slow apparent terminal elimination [Supplemental Fig. 1]). Key systemic PK data are summarized in Supplemental Table 1.

In Study 0059 and Study 0091, Day 1 mean time to C_{max} was 0.333 and 0.233 h for the 350 µg groups, respectively, and 0.317 and 0.250 h for the 700 µg groups, respectively. Increases in C_{max} were approximately dose-proportional between 22 and 700 µg in Study 0091. Renal elimination of revefenacin was limited, with mean

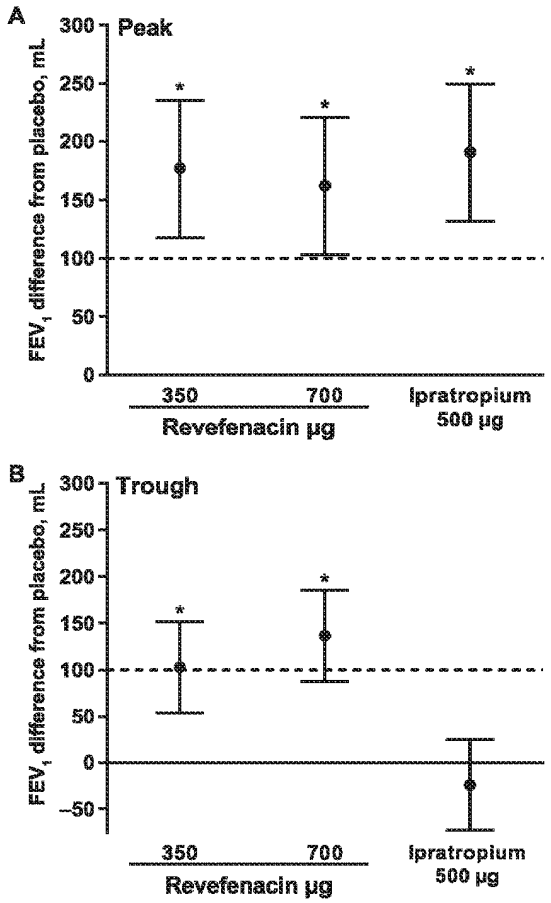

Fig. 3. FEV_1 peak and trough treatment differences from placebo (Study 0059). FEV_1 peak[a] and trough[b] values were obtained after single-dose inhalations of revefenacin or ipratropium. Data are LS mean ± 95% CI treatment differences from placebo. *$p < 0.001$. Dotted line: minimal clinically important difference [26].
[a]Peak FEV_1 is the highest value obtained between 0 and 6 h after the first dose.
[b]Trough FEV_1 is the average of values obtained at 22, 23, 24 and 25 h.
CI, confidence interval; FEV_1, forced expiratory volume in 1 s; LS, least squares.

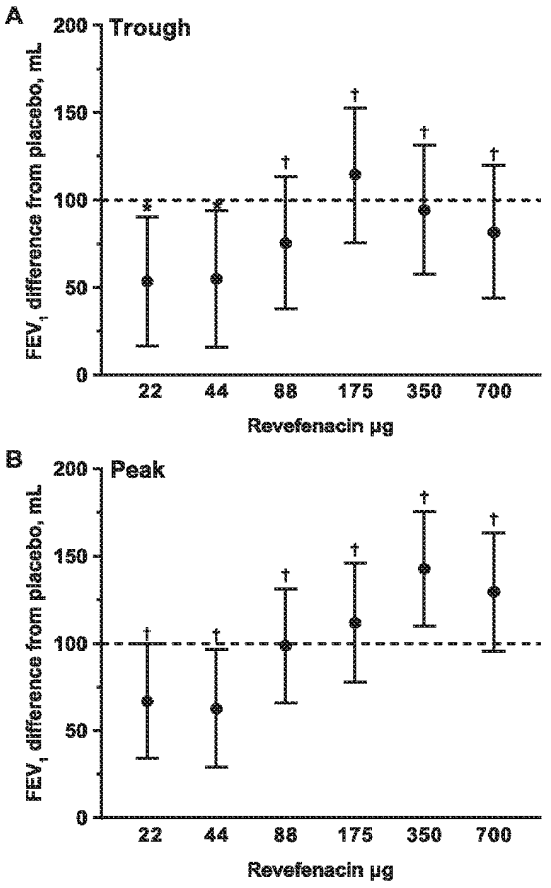

Fig. 4. FEV_1 trough and peak treatment differences from placebo (Study 0091). FEV_1 trough[a] and peak[b] and values obtained after the final dose of revefenacin 22, 44, 88, 175, 350 or 700 µg or placebo on Day 7. Data are LS mean ± 95% CI treatment differences from placebo. *$p \leq 0.006$; †$p < 0.001$. Dotted line: minimal clinically important difference [26].
[a]Trough FEV_1 is the average of values obtained at 23 and 24 h.
[b]Peak FEV_1 is the highest value obtained between 0 and 6 h after the first dose.
CI, confidence interval; FEV_1, forced expiratory volume in 1 s; LS, least squares.

cumulative amounts excreted in urine as unchanged drug of <0.2% of dose in Study 0059. Revefenacin was extensively converted to its major hydrolytic metabolite (THRX-195518) with metabolite:parent ratios for AUC_{0-t} at 350 and 700 µg of approximately 4- to 6-fold in Study 0059, and approximately 3- to 6-fold at doses ≥175 µg in Study 0091 (Day 7), respectively.

With multiple-dose administration in Study 0091, mean Day 7 $t_{1/2}$ values ranged from 22.3 to 25.3 h across dose levels. Limited accumulation (≤1.55-fold) of either revefenacin or its metabolite was observed in plasma, and steady-state concentrations were achieved by Day 7. No statistically significant pharamcodynamic effect (i.e. as a result of possible incomplete washout of the metabolite) was carried over between treatment periods.

3.4. Safety and tolerability

Revefenacin was well tolerated overall. AEs were generally mild and occurred with similar frequencies in all treatment groups in

Table 2
FEV_1 outcomes over the 24-h post-dose period (Study 0059; MPP population, $N = 32$).

	Placebo	Revefenacin		Ipratropium 500 µg
		350 µg	700 µg	
Day 1 peak (0–6 h) FEV_1, mL				
LS mean (SE)	1676.7 (30.1)	1853.5 (30.1)	1838.9 (30.1)	1867.3 (30.1)
LS mean treatment difference (95% CI) vs placebo		176.8 (117.9, 235.7)	162.2 (103.2, 221.1)	190.6 (131.7, 249.5)
p value vs placebo		<0.001	<0.001	<0.001
Day 1 trough FEV_1change, mL				
LS mean (SE)	1533.8 (22.4)	1636.6 (22.4)	1670.4 (22.4)	1509.6 (22.4)
LS mean treatment difference (95% CI) vs placebo		102.8 (54.1, 151.5)	136.6 (87.8, 185.3)	−24.2 (−72.9, 24.6)
p value vs placebo		<0.001	<0.001	<0.001

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; LS, least squares; MPP, modified per protocol; SE, standard error.

Table 3
Key FEV_1 outcomes in multiple dose study (Study 0091; ITT population).

	Placebo	Revefenacin					
		22 μg	44 μg	88 μg	175 μg	350 μg	700 μg
Day 1 peak (0–6 h) FEV_1 change from baseline, mL							
n	58	38	36	39	35	39	35
LS mean (SE)	132.4 (15.41)	199.5 (17.47)	195.2 (17.78)	231.2 (17.29)	244.4 (17.92)	275.3 (17.32)	262.0 (17.89)
LS mean treatment difference (95% CI) vs placebo	NA	67.1 (34.1, 100.0)	62.7 (28.9, 96.6)	98.8 (66.1, 131.4)	111.9 (78.1, 145.8)	142.8 (110.0, 175.7)	129.6 (95.7, 163.5)
p value vs placebo		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Day 7 trough FEV_1 change from baseline, mL							
n	56	37	32	35	33	38	35
LS mean (SE)	37.8 (16.93)	91.2 (19.21)	92.8 (20.25)	113.1 (19.55)	151.9 (19.99)	132.2 (19.02)	119.4 (19.54)
LS mean treatment difference (95% CI) vs placebo	NA	53.5 (16.5, 90.5)	55.0 (15.9, 94.1)	75.4 (37.7, 113.0)	114.2 (75.7, 152.6)	94.4 (57.7, 131.1)	81.6 (43.8, 119.5)
p value vs placebo		0.006	0.006	<0.001	<0.001	<0.001	<0.001
Day 7 weighted mean FEV_1 $AUC_{(0–12h)}$, mL							
n	ND	38	36	36	34	39	36
LS mean (SE)		1526.1 (17.91)	1523.2 (18.24)	1538.4 (18.23)	1580.5 (18.59)	1565.2 (17.78)	1548.9 (18.21)
Day 7 weighted mean FEV_1 $AUC_{(12–24h)}$, mL							
n	ND	38	36	36	34	39	36
LS mean (SE)		1472.5 (17.27)	1491.3 (17.62)	1496.5 (17.60)	1547.4 (17.98)	1527.3 (17.14)	1506.4 (17.59)
FEV_1 $AUC_{(12–24h)}$/FEV_1 $AUC_{(0–12h)}$		0.965	0.979	0.973	0.979	0.976	0.973
Day 7 weighted mean FEV_1 $AUC_{(0–24h)}$, change from baseline, mL							
n	57	38	36	36	34	39	36
LS mean (SE)	12.7 (14.85)	95.9 (16.65)	103.5 (16.96)	114.4 (16.95)	160.4 (17.28)	142.7 (16.53)	124.7 (16.93)
LS mean treatment difference (95% CI) vs placebo		83.2 (52.3, 114.2)	90.9 (59.1, 122.7)	101.8 (70.2, 133.3)	147.7 (115.5, 179.9)	130.1 (99.2, 160.9)	112.0 (80.5, 143.5)
p value vs placebo		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Responders, n (%) patients with increase in FEV_1 Day 7 trough of							
≥100 mL	11 (18.6)	16 (40.0)	13 (33.3)	20 (51.3)	21 (53.8)	25 (64.1)	16 (40.0)
≥150 mL	6 (10.2)	7 (17.5)	11 (28.2)	15 (38.5)	10 (25.6)	19 (48.7)	12 (30.0)

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FEV_1 $AUC_{0–12h}$, area under the FEV_1-time curve from time 0–12 h post dose; FEV_1 $AUC_{12–24h}$, area under the FEV_1-time-concentration curve from time 12–24 h post dose; FEV_1 $AUC_{0–24h}$, area under the FEV_1-time-concentration curve from time 0–24 h; ITT, intent to treat; LS, least squares; SE, standard error.

both studies (Table 4). No clinically significant anti-muscarinic class effects such as dry mouth, urinary retention, tachycardia or acute closed-angle glaucoma were observed.

Following single-dose administrations in Study 0059, the two most common AEs in all groups were headache ($n = 9$ (28.1%)) and dyspnea ($n = 6$ (18.8%)). No serious AEs or AEs leading to study drug discontinuation were reported. No clinically significant changes in laboratory data or QTc were observed.

Similar safety data were noted in the multiple-dose study (Study 0091). The three most common AEs in all treatment groups were dyspnea, headache and cough. Three patients each experienced a serious AE, five patients discontinued study drug due to AEs and three patients experienced AEs associated with abnormal blood pressure; none of these events was considered by the investigator to be related to study drug. No clinically meaningful changes in clinical laboratory data or ECG were observed.

4. Discussion

In two distinct phase 2 studies, inhalation of once-daily revefenacin administered via nebulizer resulted in a rapid onset of bronchodilation that was evident within the first hour post dose and demonstrated an onset time and peak effect that were similar to those achieved with ipratropium (Study 0059). In addition, this bronchodilator effect for revefenacin lasted for up to 24 h post dose, in contrast to ipratropium, which showed no evidence of bronchodilation from 12 to 24 h post dose.

The general design of the revefenacin studies reported here in terms of the crossover design and sample size is broadly consistent with that of other clinical trials evaluating the magnitude and duration of effect of long-acting bronchodilators at an early stage of clinical development [18–25]. The studies reported here provide information on dose response that can be used to select the most appropriate doses for Phase 2 and 3 clinical trials. A bronchodilator effect of 100 mL or greater has previously been suggested as a minimal clinically important difference (MCID) for FEV_1 [26]. This threshold was reached for both peak and trough FEV_1 after single revefenacin doses of 350 μg and 700 μg in Study 0059. Study 0091 investigated a wider dose response range after 7 days treatment; for peak FEV_1, revefenacin doses from 88 to 700 μg achieved the MCID threshold, indicating that lower doses may be sub-therapeutic. The trough FEV_1 results suggested that the dose response flattens around a revefenacin dose of 175 μg. The mean improvement in trough FEV_1 with revefenacin 88 μg compared to placebo was approximately 75 mL, a value below the suggested MCID threshold. However, responder analysis demonstrated that 51.3% of patients reached this threshold with revefenacin 88 μg, compared to 18.6% with placebo. Further clinical trials of longer duration and with larger sample sizes are being conducted to further define the optimum dose for clinical practice, incorporating symptom assessments as well as lung function.

The PK profile of revefenacin was consistent with its pharmacodynamic profile. In both studies, revefenacin demonstrated low plasma concentrations after inhaled administration. Parent drug was extensively converted to its major hydrolytic metabolite, consistent with high systemic clearance and a lack of systemic anti-muscarinic activity observed in the studies. The long apparent plasma $t_{1/2}$ of approximately 22–25 h indicates a steady, low-level clearance of drug from the airway tissue, consistent with long duration of action in that compartment. In Study 0059, although accumulation of revefenacin or its major metabolite was minimal with repeated administration, measurable quantities of revefenacin were apparent in plasma samples 7 days post last dose, along with a detectable statistical carryover effect in FEV_1 parameters. As a

Table 4
Summary of AEs by study and treatment administered (safety populations).

Study 0059	Placebo ($N = 32$)	Ipratropium ($N = 32$)	Revefenacin	
			350 μg ($N = 32$)	700 μg ($N = 32$)
Any AE, n (%)	16 (50)	23 (71.9)	11 (34.4)	12 (37.5)
Any serious AE, n (%)	0	0	0	0
AEs leading to study drug interruption or discontinuation, n (%)	0	0	0	0
AEs reported by ≥2 patients overall,[a] n (%)				
Headache	6 (18.8)	2 (6.3)	2 (6.3)	3 (9.4)
Dyspnea	3 (9.4)	4 (12.5)	0	2 (6.3)
Nasal congestion	1 (3.1)	0	1 (3.1)	0
Nasopharyngitis	1 (3.1)	1 (3.1)	0	0
ECG T wave peaked	1 (3.1)	1 (3.1)	2 (6.3)	1 (3.1)
Gout	1 (3.1)	1 (3.1)	1 (3.1)	1 (3.1)

Study 0091	Placebo ($N = 61$)	Revefenacin					
		22 μg ($N = 41$)	44 μg ($N = 39$)	88 μg ($N = 40$)	175 μg ($N = 37$)	350 μg ($N = 41$)	700 μg ($N = 37$)
Any AE, n (%)	33 (54.1)	19 (46.3)	18 (46.2)	19 (47.5)	17 (45.9)	16 (39.0)	14 (37.8)
Any serious AE, n (%)	1 (1.6)	2 (4.9)	0	0	0	0	0
AEs leading to study drug interruption or discontinuation, n (%)	1 (1.6)	2 (4.9)	0	1 (2.5)	1 (2.7)	0	0
AEs in ≥2 patients with any treatment, n (%)							
Headache	9 (14.8)	3 (7.3)	2 (5.1)	3 (7.5)	4 (10.8)	3 (7.3)	5 (13.5)
Cough	1 (1.6)	2 (4.9)	1 (2.6)	2 (5.0)	2 (5.4)	2 (4.9)	2 (5.4)
Dyspnea	4 (6.6)	1 (2.4)	1 (2.6)	1 (2.5)	2 (5.4)	2 (4.9)	1 (2.7)
Back pain	0	2 (4.9)	0	1 (2.5)	1 (2.7)	1 (2.4)	0
Rash	0	1 (2.4)	1 (2.6)	0	2 (5.4)	0	1 (2.7)
COPD[b]	0	1 (2.4)	0	3 (7.5)	0	0	0
Fatigue	0	2 (4.9)	2 (5.1)	0	0	0	0
Nasopharyngitis	2 (3.3)	1 (2.4)	1 (2.6)	0	0	0	0
Nausea	1 (1.6)	0	2 (5.1)	0	1 (2.7)	0	0
Oropharyngeal pain	0	0	1 (2.6)	1 (2.5)	2 (5.4)	0	0
Contusion	0	2 (4.9)	1 (2.6)	0	0	0	0
Hematoma	1 (1.6)	0	0	2 (5.0)	0	0	0
Rhinorrhea	0	0	2 (5.1)	0	1 (2.7)	0	0
Catheter site pain	0	0	2 (5.1)	0	0	0	0
Foot fracture	0	0	2 (5.1)	0	0	0	0
Hypotension	0	0	2 (5.1)	0	0	0	0
Vertigo	0	0	0	2 (5.0)	0	0	0

AE, adverse event, COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram.
[a] AEs (by preferred term) occurring in two or more patients regardless of treatment received are reported here; note that each patient received more than one treatment. Some AEs shown here may have occurred in the same patient during two or more treatment periods and are reported here during each treatment period in which it occurred.
[b] Worsening of COPD.

consequence of this observation, the washout period in Study 0091 was increased, which resulted in the absence of a discernible carryover pharmacodynamic effect in Study 0091.

The pharmacodynamic and PK results in both studies were accompanied by a favorable safety and tolerability profile, with no indication of systemic anti-cholinergic effects such as dry mouth, urinary retention, tachycardia or acute closed-angle glaucoma [27]. In addition, AE rates were similar between the revefenacin and placebo treatment periods. The safety profile is supported by pre-clinical studies that revealed revefenacin's superior functional lung selectivity index (ratio of bronchoprotective vs anti-sialagogue [diminished saliva flow] potency) compared with either glycopyrronium or tiotropium, with dose-dependent, 24-h bronchoprotection that was maintained after 7 days of once-daily dosing in animal models of bronchoconstriction [10].

In line with many short-term crossover studies of novel bronchodilator drugs, we enrolled patients with a pre-defined magnitude of reversibility to short-acting bronchodilator at baseline. This has the potential to enrich the study population with patients more likely to respond to therapy, which may be considered a limitation of the study design, but on the other hand is useful for evaluating the pharmacologic dose response. Longer-term studies are being completed in a broader patient population including 12- and 52-week efficacy and safety studies in patients with moderate to very severe COPD [12,13].

5. Conclusion

The pharmacodynamic, PK and safety results reported here for revefenacin in two phase 2 clinical trials demonstrate both a rapid onset and sustained duration of bronchodilator effect, suggesting that revefenacin holds promise as a potential once-daily nebulized treatment for COPD, and support its further evaluation in studies involving a large population of patients with COPD over an extended treatment period.

Trial registration

Study 0059 (Australian New Zealand Clinical Trial Registry identifier: U1111-1120-8290); and Study 0091 (Clinicaltrials.gov Registry identifier: NCT01704404).

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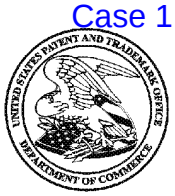
Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pupt.2017.10.003.

References

[1] Global initiative for chronic obstructive lung disease (GOLD). http://goo.gl/RQ3a, 2016. (Accessed 4 May 2016).
[2] J.L. Lopez-Campos, W. Tan, J.B. Soriano, Global burden of COPD, Respirology 21 (1) (2016) 14–23.
[3] M. Cazzola, C. Page, M.G. Matera, Long-acting muscarinic receptor antagonists for the treatment of respiratory disease, Pulm. Pharmacol. Ther. 26 (3) (2013) 307–317.
[4] A.S. Melani, Long-acting muscarinic antagonists, Expert Rev. Clin. Pharmacol. 8 (4) (2015) 479–501.
[5] M. Bonini, O.S. Usmani, The importance of inhaler devices in the treatment of COPD, COPD Res. Pract. 1 (1) (2015) 1–8.
[6] A. Sharafkhaneh, R.A. Wolf, S. Goodnight, N.A. Hanania, B.J. Make, D.P. Tashkin, Perceptions and attitudes toward the use of nebulized therapy for COPD: patient and caregiver perspectives, COPD 10 (4) (2013) 482–492.
[7] P. Quinet, C.A. Young, F. Hertier, The use of dry powder inhaler devices by elderly patients suffering from chronic obstructive pulmonary disease, Ann. Phys. Rehabil. Med. 53 (2) (2010) 69–76.
[8] Theravance Biopharma completes enrollment in all three Phase 3 clinical studies of revefenacin (TD-4208) for treatment of chronic obstructive pulmonary disease (COPD). https://goo.gl/o81rmL, 2016. (Accessed 17 October 2017).
[9] D.P. Tashkin, A review of nebulized drug delivery in COPD, Int. J. Chron. Obstruct. Pulmon. Dis. 11 (2016) 2585–2596.
[10] M.T. Pulido-Rios, A. McNamara, G.P. Obedencio, Y. Ji, S. Jaw-Tsai, W.J. Martin, S.S. Hegde, In vivo pharmacological characterization of TD-4208, a novel lung-selective inhaled muscarinic antagonist with sustained bronchoprotective effect in experimental animal models, J. Pharmacol. Exp. Ther. 346 (2) (2013) 243–250.
[11] T. Steinfeld, M. Pulido-Rios, K. Chin, K. King, J. Huang, T. Lee, J. Jasper, Y. Ji, S. Hegde, M. Mammen, In vitro characterization of TD-4208, a lung-selective and long-acting muscarinic antagonist bronchodilator, Am. J. Respir. Crit. Care Med. 179 (2009) A4553 [Abstract].
[12] K. Pudi, S. Pendyala, C. Barnes, E. Moran, B. Haumann, E. Kerwin, Trials in progress: two 12-week, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials of a nebulized long-acting muscarinic antagonist (revefenacin) in study participants with moderate to very severe COPD, Chest 150 (4_S) (2016) 825A [Abstract].
[13] L. DeLaCruz, S. Pendyala, C. Barnes, E. Moran, B. Haumann, G. Feldman, Trial in progress: a 52-week, randomized, double-blind, placebo-controlled, parallel-group phase 3 trial to evaluate the safety and tolerability of a nebulized long-acting muscarinic antagonist (revefenacin) in study participants with COPD, Chest 150 (4_S) (2016) 866A [Abstract].
[14] A phase 2, randomized, double-blind, crossover study to examine the pharmacodynamics, safety and tolerability, and pharmacokinetics of single doses of TD-4208 in subjects diagnosed with chronic obstructive pulmonary disease, in: Australia New Zealand Clinical Trial Registry [Internet], 2011. New South Wales, Australia. Universal Trial Number (UTN): U1111-1120-8290, http://bit.ly/2iLmEen. (Accessed 30 January 2017).
[15] 7 Days of TD−4208 in subjects with chronic obstructive pulmonary disease, in: ClinicalTrials.gov [Internet], National Library of Medicine (US), Bethesda (MD), 2012. Identifier: NCT01704404, http://bit.ly/2j4WuiY. (Accessed 3 January 2017).
[16] ICH, Integrated addendum to ICH harmonised guideline: guideline for good clinical practice E6 (R2). https://goo.gl/CF0mR3, 2015. (Accessed 25 July 2016).
[17] WMA declaration of Helsinki – ethical principles for medical research involving human subjects , JAMA 310 (20) (2013) 2191–2194.
[18] K.M. Beeh, C. LaForce, M. Gahlemann, A. Wenz, R. Toorawa, M. Rezar, Randomised, double-blind, placebo-controlled crossover study to investigate different dosing regimens of olodaterol delivered via Respimat® in patients with moderate to severe persistent asthma, Respir. Res. 16 (2015) 87.
[19] R. Fuhr, H. Magnussen, K. Sarem, A.R. Llovera, A.M. Kirsten, M. Peiques, C.F. Caracta, G.E. Garcia, Efficacy of aclidinium bromide 400 mug twice daily compared with placebo and tiotropium in patients with moderate to severe COPD, Chest 141 (3) (2012) 745–752.
[20] M.R. Maleki-Yazdi, E. Beck, A.L. Hamilton, L. Korducki, P. Koker, C. Fogarty, A randomised, placebo-controlled, Phase II, dose-ranging trial of once-daily treatment with olodaterol, a novel long-acting beta2-agonist, for 4 weeks in patients with chronic obstructive pulmonary disease, Respir. Med. 109 (5) (2015) 596–605.
[21] D. Singh, H. Magnussen, A. Kirsten, S. Mindt, C. Caracta, B. Seoane, D. Jarreta, G.E. Garcia, A randomised, placebo- and active-controlled dose-finding study of aclidinium bromide administered twice a day in COPD patients, Pulm. Pharmacol. Ther. 25 (3) (2012) 248–253.
[22] J. Vestbo, C. Vogelmeier, J. Creemers, M. Peiques, A. Ribera, E.G. Gil, Onset of effect of aclidinium, a novel, long-acting muscarinic antagonist, in patients with COPD, COPD 7 (5) (2010) 331–336.
[23] G.F. Joos, J.L. Aumann, C. Coech, L. Korducki, A.L. Hamilton, C. Kunz, R. Aalbers, A randomised, double-blind, four-way, crossover trial comparing the 24-h FEV1 profile for once-daily versus twice-daily treatment with olodaterol, a novel long-acting beta2-agonist, in patients with chronic obstructive pulmonary disease, Respir. Med. 109 (5) (2015) 606–615.
[24] D. Singh, W. Schroder-Babo, G. Cohuet, A. Muram, F. Bonnet-Genod, S. Peruzzelli, M. Hoffmann, Z. Siergiejko, The bronchodilator effects of extrafine glycopyrronium added to combination treatment with beclometasone dipropionate plus formoterol in COPD: a randomised crossover study (the TRIDENT study), Respir. Med. 114 (2016) 84–90.
[25] D. Singh, A. Ravi, F. Reid, H. Buck, G. O'Connor, G. Down, Bronchodilator effects, pharmacokinetics and safety of PSK1002-68, a novel glycopyrronium bromide formulation, in COPD patients: a randomised crossover study, Pulm. Pharmacol. Ther. 37 (2016) 9–14.
[26] P.W. Jones, K.M. Beeh, K.R. Chapman, M. Decramer, D.A. Mahler, J.A. Wedzicha, Minimal clinically important differences in pharmacological trials, Am. J. Respir. Crit. Care Med. 189 (3) (2014) 250–255.
[27] M. Cazzola, C.P. Page, L. Calzetta, M.G. Matera, Pharmacology and therapeutics of bronchodilators, Pharmacol. Rev. 64 (3) (2012) 450–504.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/555,216	08/29/2019	CHRISTOPHER NOEL BARNES	P-340-US1	8316

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EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
07/08/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patent@theravance.com
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Office Action Summary	Application No. 16/555,216	Applicant(s) BARNES et al.	
	Examiner Leslie A Royds Draper	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 18 March 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-53 is/are pending in the application.

5a) Of the above claim(s) 9-13 and 22-26 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-8,14-21 and 27-53 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 25Nov19;11Dec19;10Jun21.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1-53 are presented for examination.

Acknowledgement is made of Applicant's claim for benefit under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018.

Requirement for Restriction/Election

Applicant's election **without traverse** of (i) a muscarinic antagonist as the single disclosed species of bronchodilator, and (ii) revefenacin as the single disclosed species of muscarinic antagonist, to which examination on the merits will be confined, as stated in the reply filed March 18, 2021, is acknowledged by the Examiner.

Therefore, for the reasons above and those made of record at p.2-4 of the Office Action dated January 19, 2021, the requirement remains proper and is hereby made **FINAL**.

Claims 9-13 and 22-26 are withdrawn from consideration pursuant to 37 C.F.R. §1.142(b) as being directed to non-elected subject matter.

The claims that are drawn to the elected species are claims 1-8, 14-21 and 27-53 and such claims are herein acted on the merits *infra*.

Information Disclosure Statements

Applicant's Information Disclosure Statements filed November 25, 2019 (five pages), December 11, 2019 (three pages), and June 10, 2021 (two pages) have each been received and entered into the present application. As reflected by the attached, completed copies of form PTO/SB/08A (10 pages total), the Examiner has considered the cited references, with the exception of Non-Patent Literature Citations 1 and 11 on the November 25, 2019 statement, which do not identify the date of publication, publisher, author (if any), relevant pages of the publication, and place of publication. As a result, these Citations 1 and 11 fail to comply with the provisions of 37 C.F.R. §1.97, §1.98 and MPEP §609 because 37 C.F.R.

§1.98(b)(5) explicitly requires that "[e]ach publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication", thereby clearly establishing that such information pertaining to the publisher, author (if any), relevant pages, and date and place of publication must be provided. Such documents have been placed in the application file, but the information referred to therein has not been considered as to the merits.

Applicant is advised that the date of any re-submission of any item of information contained in this IDS or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 C.F.R. §1.97(e). See MPEP §609.05(a).

Priority

Acknowledgement is made of Applicant's claim for benefit under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018. Applicant is reminded that a later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. §112(a) or the first paragraph of pre-AIA 35 U.S.C. §112, except for the best mode requirement. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of prior-filed U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018, appears to provide adequate written support and/or enabling guidance as required under 35 U.S.C. §112(a) or the first paragraph of pre-AIA 35 U.S.C. §112 for the full scope of subject matter provided for in claims 1-8, 14-21 and 27-53 presently under examination.

Accordingly, the effective filing date of claims 1-8, 14-21 and 27-53 is August 30, 2018 (the filing date of the '805 provisional application).

The Examiner will revisit the issue of priority as necessary each time the claims are amended.

Claim Rejections - 35 USC § 101 – Patent Eligibility

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claims 40-53 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a judicial exception without significantly more.

Analysis of subject-matter eligibility under 35 U.S.C. §101 requires consideration of the following issues: (1) whether the claim is directed to one of the four categories of subject matter recited in §101; (2a) whether the claim recites an abstract idea, law of nature, or natural phenomenon (which includes natural products); (2b) whether the claim recites additional elements that integrate the judicial exception into a practical application; and (3) whether the claim as a whole recites additional elements that amount to significantly more than the judicial exception. See the 2019 Revised Patent Subject Matter Eligibility Guidance (2019 PEG), published in the Federal Register (Vol.84, No.4, on Monday, January 7, 2019), as well as the most recently issued October 2019 Patent Eligibility Guidance Update (October 2019 Update).

The claims are analyzed for patent eligibility in accordance with their broadest reasonable interpretation. MPEP §2106(II) ("It is essential that the broadest reasonable interpretation (BRI) of the claim be established prior to examining a claim for eligibility. The BRI sets the boundaries of the coverage sought by the claim and will influence whether the claim seeks to cover subject matter that is beyond the four statutory categories or encompasses subject matter that falls within the exceptions").

Instant Claims 40-46

Claim Interpretation: Under the broadest reasonable interpretation standard, the terms of the claim are presumed to have their plain meaning consistent with the specification as it would be interpreted by one of ordinary skill in the art. MPEP §2111. The broadest reasonable interpretation of instant claim 40 is a method for selecting a patient having chronic obstructive pulmonary disease (COPD) for treatment with a bronchodilator administered via nebulizer comprising (a) determining the peak inspiratory flow rate (PIFR) of the patient, (b) determining the percent predicted force expiratory volume in one second (% predicted FEV1) of the patient, and (c) selecting the patient for treatment with a

bronchodilator administered via nebulizer if the patient has a PIFR of < about 60 L/min and % predicted FEV1 < about 50%. The patient of the recited method is defined as having COPD, but no treatment of the subject with the bronchodilator is actually required.

Step 1: The claim is directed to a process, which is one of the statutory categories of invention (*Step 1: YES*).

Step 2A, Prong One: As explained in MPEP §2106.04(II) and the October 2019 Update, a claim "recites" a judicial exception when the judicial exception is "set forth" or "described" in the claim. Instant claim 40 recites step (c) directed to "selecting the patient for treatment with a bronchodilator administered using a nebulizer if the patient has a [PIFR] less than about 60 L/min and a percent predicted force expiratory volume in one second less than about 50 percent", which has a BRI that requires a determination of whether the subject would be suitable for treatment with a bronchodilator using a nebulizer by observing the numerical values of the patient's PIFR and % predicted FEV1 – a process that can practically be performed in the human mind. This limitation, therefore, is directed to a type of "mental process" grouping of abstract ideas (2019 PEG Section II). Accordingly, the claim recites a judicial exception (an abstract idea that falls within the mental process groupings in the 2019 PEG).

As such, the analysis must proceed to *Step 2A, Prong Two*.

Step 2A, Prong Two: This part of the eligibility analysis evaluates whether the claim as a whole integrates the recited judicial exception into a practical application of the exception. This evaluation is performed by (a) identifying whether there are any additional elements recited in the claim beyond the judicial exception, and (b) evaluating those additional elements individually and in combination to determine whether the claim as a whole integrates the exception into a practical application. 2019 PEG Section III(A)(1), 84 Fed. Reg. at 54-55. Applicant's instant claim 40 recites step (a) of "determining the [PIFR] of the patient". Although step (a) requires a determination of the patient's PIFR, this determining step is performed in order to gather data for the mental analysis step, and is a necessary precursor for all uses of the recited exception. Applicant's instant claim 40 also recites step (b) of "determining the [% predicted FEV1] of the patient". Although step (b) requires a determination of the patient's % predicted FEV1, this determining step is performed in order to gather data for the mental analysis step, and is a

necessary precursor for all uses of the recited exception. Steps (a)-(b), therefore, constitute extra-solution activity and fail to integrate the judicial exception into a practical application (*Step 2A, Prong Two*).

Step 2B: This part of the eligibility analysis evaluates whether the claim as a whole amounts to significantly more than the recited exception (i.e., whether any additional element, or combination of additional elements, adds an inventive concept to the claim). MPEP §2106.05. As explained with respect to Step 2A, Prong Two, the claim recites additional elements in steps (a) and (b), which amount to extra-solution activity. Under the 2019 PEG, however, a conclusion that an additional element is insignificant extra-solution activity in Step 2A should be re-evaluated in Step 2B (2019 PEG Section III(B), 84 Fed. Reg. at 56). At Step 2B, the evaluation of the insignificant extra-solution activity consideration takes into account whether or not the extra-solution activity is well-known. MPEP §2106.05(g). Here, Applicant's steps (a) and (b) constitute well-understood, routine, and conventional activity previously known to the industry. See, e.g., Ghosh et al. ("Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2017; 30(6):381-387, cited by Applicant on the 11/25/19 IDS), Vestbo et al. ("Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease", *Am J Respir Crit Care Med*, 2013; 187(4):347-365) and Gerhart et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016), which each document the well-understood, routine and conventional nature of spirometry to measure pulmonary function and airflow limitation (e.g., PIFR, % predicted FEV1) in COPD patients.

Also, the correlation of such parameters to a specific type of delivery system for bronchodilator therapy (in this case, a nebulizer) was also well-understood, routine and conventional given that severely impaired lung function – as evidenced by reduced PIFR and % predicted FEV1 – was well-known to inhibit effective use of conventional devices, such as dry powder inhalers (DPIs), for medication dispersal in the lung and was generally considered more responsive to nebulized therapies. See, e.g., Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS), Ghosh et al. ("Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers", *Journal of Aerosol*

Medicine and Pulmonary Drug Delivery, 2017; 30(6):381-387, cited by Applicant on the 11/25/19 IDS), and Mahler et al. ("Peak Inspiratory Flow Rate as a Criterion for Dry Powder Inhaler Use in Chronic Obstructive Pulmonary Disease", *Ann Am Thorac Soc*, 2017 July; 14(7):1103-1107, cited by Applicant on the 11/25/19 IDS). Thus, steps (a)-(b) do not amount to significantly more (*Step 2B: NO*).

As claims 41-43 seek only to further define the PIFR and/or % predicted FEV1 parameters used for patient selection, they are subject to the same analysis as set forth above with regard to claim 40.

As claims 44-46 seek only to further define the bronchodilator for which the patient is selected for treatment (but not actually treated with the bronchodilator), they are subject to the same analysis as set forth above with regard to claim 40.

Instant Claims 47-53

Claim Interpretation: Under the broadest reasonable interpretation standard, the terms of the claim are presumed to have their plain meaning consistent with the specification as it would be interpreted by one of ordinary skill in the art. MPEP §2111. The broadest reasonable interpretation of instant claim 47 is a method for selecting a nebulizer as the inhalation delivery device for administering a bronchodilator to a patient having COPD comprising (a) determining the PIFR of the patient, (b) determining the % predicted FEV1 of the patient, and (c) selecting a nebulizer to administer a bronchodilator to the patient if the patient has a PIFR of < about 60 L/min and a % predicted FEV1 of < about 50%. The patient of the recited method is defined as having COPD, but no treatment of the subject with the bronchodilator is actually required.

Step 1: The claim is directed to a process, which is one of the statutory categories of invention (*Step 1: YES*).

Step 2A, Prong One: As explained in MPEP §2106.04(II) and the October 2019 Update, a claim "recites" a judicial exception when the judicial exception is "set forth" or "described" in the claim. Instant claim 47 recites step (c) directed to "selecting a nebulizer to administer a bronchodilator to the patient if the patient has a PIFR less than about 60 L/min and a percent predicted force expiratory volume in one second less than about 50 percent", which has a BRI that requires a determination of whether the subject

would be suitable for treatment with a bronchodilator using a nebulizer by observing the numerical values of the patient's PIFR and % predicted FEV1 – a process that can practically be performed in the human mind. This limitation, therefore, is directed to a type of "mental process" grouping of abstract ideas (2019 PEG Section II). Accordingly, the claim recites a judicial exception (an abstract idea that falls within the mental process groupings in the 2019 PEG).

As such, the analysis must proceed to *Step 2A, Prong Two*.

Step 2A, Prong Two: This part of the eligibility analysis evaluates whether the claim as a whole integrates the recited judicial exception into a practical application of the exception. This evaluation is performed by (a) identifying whether there are any additional elements recited in the claim beyond the judicial exception, and (b) evaluating those additional elements individually and in combination to determine whether the claim as a whole integrates the exception into a practical application. 2019 PEG Section III(A)(1), 84 Fed. Reg. at 54-55. Applicant's instant claim 47 recites step (a) of "determining the [PIFR] of the patient". Although step (a) requires a determination of the patient's PIFR, this determining step is performed in order to gather data for the mental analysis step, and is a necessary precursor for all uses of the recited exception. Applicant's instant claim 47 also recites step (b) of "determining the [% predicted FEV1] of the patient". Although step (b) requires a determination of the patient's % predicted FEV1, this determining step is performed in order to gather data for the mental analysis step, and is a necessary precursor for all uses of the recited exception. Steps (a)-(b), therefore, constitute extra-solution activity and fail to integrate the judicial exception into a practical application (*Step 2A, Prong Two*).

Step 2B: This part of the eligibility analysis evaluates whether the claim as a whole amounts to significantly more than the recited exception (i.e., whether any additional element, or combination of additional elements, adds an inventive concept to the claim). MPEP §2106.05. As explained with respect to Step 2A, Prong Two, the claim recites additional elements in steps (a) and (b), which amount to extra-solution activity. Under the 2019 PEG, however, a conclusion that an additional element is insignificant extra-solution activity in Step 2A should be re-evaluated in Step 2B (2019 PEG Section III(B), 84 Fed. Reg. at 56). At Step 2B, the evaluation of the insignificant extra-solution activity consideration takes into account whether or not the extra-solution activity is well-known. MPEP §2106.05(g). Here, Applicant's

steps (a) and (b) constitute well-understood, routine, and conventional activity previously known to the industry. See, e.g., Ghosh et al. ("Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2017; 30(6):381-387, cited by Applicant on the 11/25/19 IDS), Vestbo et al. ("Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease", *Am J Respir Crit Care Med*, 2013; 187(4):347-365) and Gerhart et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016), which each document the well-understood, routine and conventional nature of spirometry to measure pulmonary function and airflow limitation (e.g., PIFR, % predicted FEV1) in COPD patients.

Also, the correlation of such parameters to a specific type of delivery system for bronchodilator therapy (in this case, a nebulizer) was also well-understood, routine and conventional given that severely impaired lung function – as evidenced by reduced PIFR and % predicted FEV1 – was well-known to inhibit effective use of conventional devices, such as DPIs, for medication dispersal in the lung and was generally considered more responsive to nebulized therapies. See, e.g., Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS), Ghosh et al. ("Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2017; 30(6):381-387, cited by Applicant on the 11/25/19 IDS), and Mahler et al. ("Peak Inspiratory Flow Rate as a Criterion for Dry Powder Inhaler Use in Chronic Obstructive Pulmonary Disease", *Ann Am Thorac Soc*, 2017 July; 14(7):1103-1107, cited by Applicant on the 11/25/19 IDS). Thus, steps (a)-(b) do not amount to significantly more (*Step 2B: NO*).

As claims 48-50 seek only to further define the PIFR and/or % predicted FEV1 parameters used for patient selection, they are subject to the same analysis as set forth above with regard to claim 47.

As claims 51-53 seek only to further define the bronchodilator for which the patient is selected for treatment (but not actually treated with the bronchodilator), they are subject to the same analysis as set forth above with regard to claim 47.

Accordingly, claims 40-53 are directed to patent-ineligible subject matter under 35 U.S.C. §101.

Claim Rejections - 35 USC § 112(b) (Pre-AIA Second Paragraph)

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-8, 14-21 and 27-39 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

In claim 1, Applicant recites "[a] method for treating [COPD] in a patient", but it is unclear if the patient is in need of treatment for COPD, or is any patient. Clarification is required.

In claim 1, the selection of "a patient" in step (a) of the claimed method renders the claim indefinite because it is again unclear if this patient is required to exhibit COPD and the recited PIFR and % predicted FEV1, or just the recited PIFR and % predicted FEV1. Clarification is required.

In claim 7, Applicant recites that "the muscarinic antagonist is selected from aclidinium, glycopyrronium, ipratropium, revefenacin, tiotropium and umeclidinium; or a pharmaceutically acceptable salt thereof, which renders the claim indefinite because it is unclear if the recited limitation of "tiotropium and umeclidinium" is intended to circumscribe (i) the muscarinic antagonist as either tiotropium or umeclidinium individually, or (ii) the muscarinic antagonist as a combination of tiotropium with umeclidinium. Applicant's use of the conjunction "and" between the final two listed antagonists ("tiotropium and umeclidinium") implies the use of the two antagonists in combination, which appears to conflict with the recitation that "the muscarinic antagonist" is selected from any one of the subsequent options (which implies the use of a single muscarinic antagonist, not a combination thereof). Similar ambiguity exists also in claim 20, which recites substantially identical language. Clarification is required.

In claim 14, Applicant recites "[a] method for treating [COPD] in a patient", but it is unclear if the patient is in need of treatment for COPD, or is any patient. Clarification is required.

In claim 27, Applicant recites "[a] method for treating [COPD] in a patient", but it is unclear if the patient is in need of treatment for COPD, or is any patient. Clarification is required.

In claim 27, the selection of "a patient" in step (a) of the claimed method renders the claim indefinite because it is again unclear if this patient is required to exhibit COPD and the recited PIFR and % predicted FEV1, or just the recited PIFR and % predicted FEV1. Clarification is required.

As claims 2-6, 8, 15-19, 21 and 28-39 do not remedy these points of ambiguity in the claims, they must also be rejected on the same grounds.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. §112(b) (pre-AIA second paragraph) and are, thus, properly rejected.

Claim Rejections - 35 USC § 102

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

3. Claims 1, 4-5, 14, 17-18, 40, 43-44, 47 and 50-51 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[1] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2,

[1] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets

p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, forced vital capacity (FVC) and IC (inspiratory capacity) were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

In claim 1, Applicant recites "[a] method for treating [COPD] in a patient" comprising (a) selecting a patient with PIFR of < about[2] 60 L/min and % predicted FEV1 of < about 50%, and (b) administering a bronchodilator to the selected patient using a nebulizer.

In claim 4, which depends from claim 1, Applicant further limits the PIFR to about 20 L/min to < about 60 L/min, and % predicted FEV1 from about 20% to < about 50%.

In claim 5, which depends from any one of claims 1-4, Applicant defines the bronchodilator as, e.g., a β-adrenergic receptor agonist, muscarinic antagonist, etc.

Mahler et al. teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) with nebulized arformoterol solution, which was

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Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

[2] Applicant defines the term "about" as "± 10 percent of the specified value" at p.5, l.11 of the as-filed specification.

effective to improve lung function. Such teachings necessarily require selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11), followed by administration of the bronchodilator arformoterol solution via nebulizer, as required by claim 1.

The teachings of Mahler et al. also meet Applicant's narrowed limitations directed to a PIFR of about 20 L/min to < about 60 L/min, as recited in claim 4, as Mahler teaches a PIFR of 53.3 ± 5.0 L/min (48.3-58.3 L/min).

The teachings of Mahler et al. also meet Applicant's narrowed limitations directed to a % predicted FEV1 of about 20% to < about 50%, as recited in claim 4, as Mahler teaches a % predicted FEV1 of 35 ± 11 (24-46%).

In claim 14, Applicant recites "[a] method for treating [COPD] in a patient" comprising (a) determining the PIFR of the patient, (b) determining the % predicted FEV1 of the patient, (c) selecting the patient for treatment with a bronchodilator administered via nebulizer if the patient has a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%, and (d) administering the bronchodilator to the selected patient using the nebulizer.

In claim 17, which depends from claim 14, Applicant further limits the PIFR to about 20 L/min to < about 60 L/min, and % predicted FEV1 from about 20% to < about 50%.

In claim 18, which depends from any one of claims 14-17, Applicant defines the bronchodilator as, e.g., a β-adrenergic receptor agonist, muscarinic antagonist, etc.

Mahler et al. teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) with nebulized arformoterol solution, which was effective to improve lung function. Such teachings necessarily require a step of determining the patient's PIFR, determining the patient's % predicted FEV1, selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11), followed by administration of the bronchodilator arformoterol aerosol solution via nebulizer, as required by instant claim 14.

In claim 40, Applicant recites "[a] method for selecting a patient having [COPD] for treatment with a bronchodilator administered using a nebulizer" comprising (a) determining the PIFR of the patient, (b) determining the % predicted FEV1 of the patient, and (c) selecting the patient for treatment with a

bronchodilator administered via nebulizer if the patient has a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%.

In claim 43, which depends from claim 40, Applicant further limits the PIFR to about 20 L/min to < about 60 L/min, and % predicted FEV1 from about 20% to < about 50%.

In claim 44, which depends from any one of claims 40-43, Applicant defines the bronchodilator as, e.g., a β-adrenergic receptor agonist, muscarinic antagonist, etc.

Mahler et al. teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) with nebulized arformoterol solution, which was effective to improve lung function. Such teachings necessarily require a step of determining the patient's PIFR, determining the patient's % predicted FEV1, and selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) for administration of the bronchodilator arformoterol aerosol solution via nebulizer, as required by instant claim 40.

In claim 47, Applicant recites "[a] method for selecting a nebulizer as the inhalation delivery device used to administer a bronchodilator to a patient having [COPD]" comprising (a) determining the PIFR of the patient, (b) determining the % predicted FEV1 of the patient, and (c) selecting a nebulizer to administer a bronchodilator to the patient if the patient has a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%.

In claim 50, which depends from claim 47, Applicant further limits the PIFR to about 20 L/min to < about 60 L/min, and % predicted FEV1 from about 20% to < about 50%.

In claim 51, which depends from any one of claims 47-50, Applicant defines the bronchodilator as, e.g., a β-adrenergic receptor agonist, muscarinic antagonist, etc.

Mahler et al. teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) with nebulized arformoterol solution, which was effective to improve lung function. Such teachings necessarily require a step of determining the patient's PIFR, determining the patient's % predicted FEV1, and selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) for treatment with a nebulizer for administration of the bronchodilator arformoterol aerosol solution, as required by instant claim 47.

Therefore, instant claims 1, 4-5, 14, 17-18, 40, 43-44, 47 and 50-51 are properly anticipated under AIA 35 U.S.C. §102(a)(1).

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

4. Claims 2-3, 15-16, 41-42 and 48-49 are rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[3] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2, p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

Mahler et al. differs from the instant claims only insofar as it does not explicitly teach that the COPD patients selected for treatment with a bronchodilator administered via nebulizer exhibit PIFR of < about 50 L/min (claims 2, 15, 41, 48) or % predicted FEV1 of < about 40% (claims 3, 16, 42, 49).

In claims 2, 15, 41, and 48, Applicant further limits the PIFR to < about 50 L/min.

In claims 3, 16, 42, and 49, Applicant further limits the % predicted FEV1 to < about 40%.

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[3] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50 L/min in claims 2, 15, 41, and 48 constitutes a range of < 45-55 L/min, and < about 40% in claims 3, 16, 42, and 49 constitutes a range of < 36-44%.

Here, Mahler et al. clearly teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) with nebulized arformoterol solution, which was effective to improve lung function as measured by FEV1, FVC and IC. Such teachings necessarily require a step of determining the patient's PIFR, determining the patient's % predicted FEV1, and selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min, or a range of 48.3-58.3 L/min) and % predicted FEV1 of < about 50% (35 ± 11%, or a range of 24-46%) for treatment with a nebulizer for administration of the bronchodilator arformoterol aerosol solution.

The teachings of Mahler et al. suggest the selection of COPD patients with a PIFR of 53.3 ± 5.0 L/min, or a range of 48.3-58.3 L/min, and % predicted FEV1 of 35 ± 11%, or a range of 24-46%, which clearly meet and/or overlap the ranges recited in instant claims 2, 15, 41, and 48 (i.e., < 45-55 L/min) and instant claims 3, 16, 42, and 49 (i.e., < 36-44%). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) …" [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

5. Claims 6-8, 19-21, 45-46 and 52-53 are rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Gerhart

et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016), citing to Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS) as evidence.

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[4] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2, p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

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[4] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

Mahler et al. differs from the instant claims only insofar as it teaches the nebulized bronchodilator therapy as the β-agonist arformoterol, not the muscarinic antagonist revefenacin as claimed (claims 6-8, 19-21, 45-46 and 52-53).

Gerhart et al. teaches that there are two general categories of bronchodilator therapy for the treatment of COPD, which are (i) muscarinic antagonists, and (ii) β-adrenergic receptor agonists (p.1, para.[0006]). Gerhart et al. teaches that muscarinic antagonists are generally preferred and recommended as first-line therapy for maintenance treatment of moderate to severe COPD (p.1, para.[0006]). Gerhart et al. teaches that muscarinic antagonists are either long-acting or short-acting, with long-acting muscarinic antagonists being preferred to short-acting as a result of their superior efficacy and duration of effect (p.1, para.[0006]). Gerhart et al. teaches long-acting muscarinic antagonists with therapeutic effect lasting more than about 6 hours, including TD-4208 (p.6, para.[0047]).

Quinn et al. is cited as factual evidence that TD-4208 is synonymous with revefenacin (abstract).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in substituting the long-acting muscarinic antagonist revefenacin (TD-4208) as the nebulized bronchodilator therapy for the β-agonist arformoterol used in Mahler's method for treating COPD patients because each was known in the art as an effective bronchodilator for the treatment of COPD, as evidenced by Gerhart's teachings. The substitution, therefore, of revefenacin for the β-agonist arformoterol in Mahler's nebulized COPD therapy would have been *prima facie* obvious before the effective filing date of the claimed invention because each was known in the art at such time as an effective bronchodilator for treating COPD and, thus, would have been reasonably interchanged with one another in Mahler's method based upon this functional equivalency. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-96, quoting *Sakraida v. AG Pro., Inc.*, 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1981) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

The ordinarily skilled artisan would have been additionally motivated to make such a substitution of the long-acting muscarinic antagonist revefenacin for the β-agonist arformoterol because Gerhart et al. teaches the particular efficacy of muscarinic antagonists in the treatment of moderate to severe COPD, of which Mahler's patients with PIFR of < 60 L/min and % predicted FEV1 of < 50% clearly constitute either moderate or severe COPD as a result of this significant limitation of airway function.

In claim 6, Applicant recites "[a] method for treating [COPD] in a patient" comprising (a) selecting a patient with PIFR of < about[5] 60 L/min and % predicted FEV1 of < about 50%, and (b) administering a bronchodilator to the selected patient using a nebulizer, wherein the bronchodilator is a muscarinic antagonist.

In claims 7-8, Applicant defines the muscarinic antagonist as revefenacin.

In claim 19, Applicant recites "[a] method for treating [COPD] in a patient" comprising (a) determining the PIFR of the patient, (b) determining the % predicted FEV1 of the patient, (c) selecting the patient for treatment with a bronchodilator administered via nebulizer if the patient has a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%, and (d) administering the bronchodilator to the selected patient using the nebulizer, wherein the bronchodilator is a muscarinic antagonist.

In claims 20-21, Applicant defines the muscarinic antagonist as revefenacin.

In claim 45, Applicant recites "[a] method for selecting a patient having [COPD] for treatment with a bronchodilator administered using a nebulizer" comprising (a) determining the PIFR of the patient, (b) determining the % predicted FEV1 of the patient, and (c) selecting the patient for treatment with a bronchodilator administered via nebulizer if the patient has a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%, wherein the bronchodilator is a muscarinic antagonist.

In claim 46, Applicant defines the muscarinic antagonist as revefenacin.

In claim 52, Applicant recites "[a] method for selecting a nebulizer as the inhalation delivery device used to administer a bronchodilator to a patient having [COPD]" comprising (a) determining the PIFR of the patient, (b) determining the % predicted FEV1 of the patient, and (c) selecting a nebulizer to

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[5] Applicant defines the term "about" as "± 10 percent of the specified value" at p.5, l.11 of the as-filed specification.

administer a bronchodilator to the patient if the patient has a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%, wherein the bronchodilator is a muscarinic antagonist.

In claim 53, Applicant defines the muscarinic antagonist as revefenacin.

Mahler et al. teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) with nebulized arformoterol solution, which was effective to improve lung function as measured by FEV1, FVC and IC. Such teachings necessarily require selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11) for administration of the bronchodilator arformoterol aerosol solution via nebulizer.

Although Mahler et al. is directed to the administration of a nebulized β-agonist bronchodilator for the treatment of the COPD patients, Gerhart et al. provides factual extrinsic evidence relevant to establishing the *prima facie* obviousness of substituting the muscarinic antagonist revefenacin for the β-agonist arformoterol for the reasons set forth above.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

6. Claims 27-34 and 39 are rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[6] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2,

[6] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of <

p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

Mahler et al. differs from the instant claims only insofar as it teaches the nebulized bronchodilator therapy as the β-agonist arformoterol, not an aqueous solution of revefenacin (claim 27), particularly wherein the composition comprising the aqueous revefenacin solution has (i) a pH of about 4.5 to about 5.5 (claim 31) or about 4.8 to about 5.2 (claim 32), or (ii) further comprises sodium chloride, citric acid and sodium citrate (claim 34).

Quinn et al. teaches the administration of the long-acting muscarinic antagonist revefenacin in doses of 22, 44, 88, 175, 350 and 700 μg in 10 mM citrate buffer in normal saline at pH 5.0 to patients with moderate to severe COPD and % predicted FEV1 of 47.2 (± 12.4) once daily for 7 days using a PARI LC Sprint jet nebulizer (abstract; col.2, para.4, p.72; Table 1, p.74). Quinn et al. observed that revefenacin was effective to provide a rapid onset and sustained duration of bronchodilator effect (col.2, para.1, p.78).

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about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in substituting an aqueous solution of the long-acting muscarinic antagonist revefenacin as the nebulized bronchodilator therapy for the β-agonist arformoterol used in Mahler's method for treating COPD patients because each was known in the art as an effective nebulized bronchodilator for the treatment of COPD, as evidenced by Quinn's teachings. The substitution, therefore, of an aqueous solution of revefenacin for the β-agonist arformoterol in Mahler's nebulized COPD therapy would have been *prima facie* obvious before the effective filing date of the claimed invention because each was known in the art at such time as an effective bronchodilator for treating COPD and, thus, would have been reasonably interchanged with one another in Mahler's method based upon this functional equivalency. "When a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." See *KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1395-96, quoting *Sakraida v. AG Pro., Inc.*, 425 U.S. 273 (1976) and *In re Fout*, 675 F.2d 297, 301 (CCPA 1981) ("Express suggestion to substitute one equivalent for another need not be present to render such substitution obvious").

In claim 27, Applicant recites "[a] method for treating [COPD] in a patient" comprising (a) selecting a patient with PIFR of < about 60 L/min and % predicted FEV1 of < about 50%, and (b) administering an aqueous solution of revefenacin to the selected patient using a nebulizer.

In claim 28, Applicant further limits the PIFR to < about 50 L/min.

In claim 29, Applicant further limits the % predicted FEV1 to < about 40%.

In claim 30, Applicant further limits the PIFR to about 20 L/min to < about 60 L/min, and % predicted FEV1 from about 20% to < about 50%.

Mahler et al. clearly teaches the treatment of 20 COPD patients with PIFR of < 60 L/min (53.3 $\pm$ 5.0 L/min) (or about 20 L/min to < about 60 L/min, as in claim 30) and % predicted FEV1 of < about 50% (35 $\pm$ 11) (or about 20% to < about 50%, as in claim 30) with nebulized arformoterol solution, which was effective to improve lung function as measured by FEV1, FVC and IC.

Such teachings necessarily require a step of determining the patient's PIFR, determining the patient's % predicted FEV1, and selecting such patients with PIFR of < about 60 L/min (53.3 ± 5.0 L/min, or a range of 48.3-58.3 L/min) and % predicted FEV1 of < about 50% (35 ± 11%, or a range of 24-46%) for treatment with a nebulizer for administration of the bronchodilator arformoterol aerosol solution.

As established above, Quinn et al. provides teachings relevant to the *prima facie* obviousness of substituting an aqueous solution of revefenacin for the arformoterol solution used in Mahler et al. for the reasons set forth above.

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50 L/min in claim 28 constitutes a range of < 45-55 L/min, and < about 40% in claim 29 constitutes a range of < 36-44%.

The teachings of Mahler et al. suggest the selection of COPD patients with a PIFR of 53.3 ± 5.0 L/min, or a range of 48.3-58.3 L/min, and % predicted FEV1 35 ± 11%, or a range of 24-46%, which clearly meet and/or overlap the ranges recited in instant claim 28 (i.e., < 45-55 L/min) and instant claim 29 (i.e., < 36-44%). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) ..." [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

In claim 31, Applicant recites that the aqueous solution has a pH of about 4.5-5.5.

In claim 32, Applicant recites that the aqueous solution has a pH of about 4.8-5.2.

In claim 33, Applicant recites that the pharmaceutical composition comprising the aqueous solution is isotonic.

In claim 34, Applicant recites that the pharmaceutical composition comprising the aqueous solution further comprises sodium chloride, citric acid and sodium citrate.

In claim 39, Applicant recites that the aqueous solution is administered using a jet nebulizer.

Quinn et al. teaches an aqueous solution of revefenacin for administration via PARI LC Sprint jet nebulizer to COPD patients, which contains citrate buffer in normal (isotonic) saline, with pH of 5.0, thereby meeting Applicant's instantly claimed requirements.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

7. Claim 35 is rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS),

as applied above to claims 27-32, 34 and 39,

further in view of Hirsh et al. (U.S. Patent Application Publication No. 2004/0045546 A1; 2004).

Mahler in view of Quinn, as applied above to claims 27-32, 34 and 39.

Mahler in view of Quinn differ from the instant claim only insofar as they do not explicitly teach that the solution is sterile (claim 35).

Hirsh et al. teaches a composition for reconstitution with sterile water or sterile saline solution prior to administration via nebulizer (p.4, para.[0027]). Hirsh et al. teaches that tonicity-adjusting agents are used to enhance the overall comfort to the patient upon administration of the reconstituted solution to the patient, further teaching that a preferred osmolality of the reconstituted inhalation solution is 275-305 mOsm/kg (p.4, para.[0027]). Hirsh et al. teaches that sterile isotonic saline solution is effectively used to achieve the desired tonicity of the reconstituted inhalation solution (p.4, para.[0027]).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in formulating Quinn's aqueous revefenacin solution in

normal saline for use in Mahler's method of treating COPD patients with sterile, isotonic saline because Hirsh et al. teaches the formulation of inhalation solutions for nebulization with sterile, isotonic saline. The skilled artisan would have been motivated to specifically employ sterile, isotonic saline for this purpose in view of the introduction of such solution directly into the lungs and the desire to minimize or eliminate contamination of such solution with microorganisms capable of causing infection. It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to formulate Quinn's bronchodilating aqueous revefenacin solution in sterile, isotonic saline to ensure sterility of the solution and to minimize or eliminate any contamination of such solution with infection-causing microorganisms, as suggested by Hirsh et al.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

8. Claims 36-38 are rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS),

as applied above to claims 27-32, 34 and 39,

further in view of Pudi et al. ("A 28-Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease", *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017).

Mahler in view of Quinn, as applied above to claims 27-32, 34 and 39.

Mahler in view of Quinn differ from the instant claims only insofar as they do not explicitly teach that the composition comprising the aqueous solution of revefenacin comprises about 20 μg/mL to about

60 μg/mL revefenacin (claim 36), about 88 μg/3 mL of revefenacin (claim 37), or about 175 μg/3 mL of revefenacin (claim 38).

Pudi et al. teaches an experimental study of 355 patients with moderate to severe COPD and mean % predicted FEV1 of 44% administered once-daily treatments of a 3 mL inhalation solution of 44, 88, 175 or 350 μg revefenacin or placebo via standard PARI LC Sprint jet nebulizer for 28 days (abstract; "Patients and Treatments", col.2, para.2-3, p.2; "Patients", col.2, para.5, p.3). Pudi et al. teaches that revefenacin at doses of ≥ 88 μg led to significant improvements in bronchodilation as measured by mean difference in baseline to day 28 trough FEV1 ("Discussion", col.1, para.1, p.8).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in formulating Quinn's aqueous revefenacin nebulization solution to comprise 88 μg in 3 mL or 175 μg in 3 mL for treatment of COPD patients in Mahler's method because Pudi et al. teaches the administration of revefenacin in a 3 mL inhalation solution via jet nebulizer in dosage amounts of 88 μg or 175 μg for the treatment of patients with moderate to severe COPD. The skilled artisan would have been motivated to formulate Quinn's aqueous revefenacin nebulization solution to comprise 88 μg in 3 mL or 175 μg in 3 mL because Pudi et al. teaches that the administration of revefenacin solution via jet nebulizer in such dosage quantities was effective to provide significant improvements in bronchodilation of subjects with moderate to severe COPD patients (as evidenced by mean % predicted FEV1 of < 50%). It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to formulate Quinn's aqueous revefenacin nebulization solution to comprise 88 μg in 3 mL or 175 μg in 3 mL for the effective treatment of COPD patients, as evidenced by Pudi's teachings.

In claim 36, Applicant recites that the pharmaceutical composition comprising the aqueous revefenacin solution comprises "about 20 μg/mL to about 60 μg/mL of revefenacin".

As Pudi's suggested dosages of 88 μg in 3 mL or 175 μg in 3 mL are equivalent to 29.33 μg per 1 mL or 58.3 μg per 1 mL, respectively, such suggested dosages as described in Pudi et al. clearly meet Applicant's instantly claimed range of "about 20 μg/mL to about 60 μg/mL of revefenacin", as recited in claim 36.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

9. Claims 1-8, 14-21, 27-32 and 36-39 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 27-30 and 35-36 of U.S. Patent Application No. 16/744,565 in view of Gerhart et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016) and Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS),

citing to Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS) as evidence.

'565 recites a nebulizer inhaler comprising a pharmaceutical composition comprising revefenacin (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable aqueous carrier

(copending claim 27). '565 further recites that the composition has a pH in the range of from 3-8 (copending claim 28), or is isotonic (copending claim 29). '565 further recites that the composition comprises about 0.05 μg/mL to about 10 mg/mL of revefenacin (or a pharmaceutically acceptable salt thereof) (copending claim 30). '565 further recites a nebulizer inhaler comprising an isotonic aqueous solution comprising about 0.05 μg/mL to about 10 mg/mL of revefenacin (or a pharmaceutically acceptable salt thereof) (copending claim 35). '565 further recites that the aqueous solution has a pH in the range of from 3-8 (copending claim 36).

'565 differs from the instant claims only insofar as it does not explicitly teach administration of the nebulized revefenacin for treating COPD in a patient having a PIFR of < about 60 L/min and % predicted FEV1 of < about 50% (claims 1, 14, 27), PIFR of < about 50 L/min (claims 2, 15, 28), % predicted FEV1 of < about 40% (claims 3, 16, 29), or PIFR of about 20 L/min to < about 60 L/min and % predicted FEV1 of about 20% to < about 50% (claims 4, 17, 30).

Gerhart et al. teaches that there are two general categories of bronchodilator therapy for the treatment of COPD, which are (i) muscarinic antagonists, and (ii) β-adrenergic receptor agonists (p.1, para.[0006]). Gerhart et al. teaches that muscarinic antagonists are generally preferred and recommended as first-line therapy for maintenance treatment of moderate to severe COPD (p.1, para.[0006]). Gerhart et al. teaches that muscarinic antagonists are either long-acting or short-acting, with long-acting muscarinic antagonists being preferred to short-acting as a result of their superior efficacy and duration of effect (p.1, para.[0006]). Gerhart et al. teaches long-acting muscarinic antagonists with therapeutic effect lasting more than about 6 hours, including TD-4208 (p.6, para.[0047]).

Quinn et al. is cited as factual evidence that TD-4208 is synonymous with revefenacin (abstract).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[7] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2, p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol

[7] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in administering the nebulized aqueous solution of revefenacin of the '565 claims for the treatment of COPD in a patient in need thereof because Gerhart et al. teaches revefenacin as a muscarinic antagonist for the treatment of COPD. The skilled artisan would have been motivated to administer the nebulized aqueous solution of revefenacin of the '565 claims for treating COPD in a patient in need thereof because Gerhart et al. teaches muscarinic antagonists as preferred first-line therapy for maintenance treatment of moderate to severe COPD, and further teaches revefenacin as a long-acting muscarinic antagonist with therapeutic bronchodilating effect lasting more than about 6 hours. It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the '565 claims to administer the nebulized aqueous solution of revefenacin for the treatment of COPD in a patient in need thereof in view of revefenacin's established therapeutic efficacy as a long-acting muscarinic antagonist effective for the treatment of moderate to severe COPD, as evidenced by Gerhart et al.

The ordinarily skilled artisan would have also found it *prima facie* obvious to select the patient in need of treatment for COPD with the '565 nebulized aqueous solution of revefenacin by PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler et al. teaches that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11%) exhibited greater benefit from nebulized bronchodilator therapy – as compared to DPI therapy – because patients with suboptimal PIFR of < 60 L/min were generally not capable of completely inhaling dry powder bronchodilator into the lower respiratory tract and nebulized bronchodilator therapy was able to achieve deeper penetration into the lower respiratory tract without having to rely on deep, hard inhalation to overcome the internal resistance of a DPI to deaggregate the powder into fine particles.

Applicant should note that the Mahler clearly suggests the selection of COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) (or about 20 L/min to < about 60 L/min, as in claims 4, 17, and 30) and % predicted FEV1 of < about 50% (35 ± 11) (or about 20% to < about 50%, as in claims 4, 17 and 30) with nebulized bronchodilator therapy, thereby meeting the limitations of claims 1, 4, 14, 17, 27 and 30.

Regarding claims 2-3, 15-16 and 28-29:

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50 L/min in claims 2, 15 and 28 constitutes a range of < 45-55 L/min, and < about 40% in claims 3, 16 and 29 constitutes a range of < 36-44%.

The teachings of Mahler et al. suggest the selection of COPD patients with a PIFR of 53.3 ± 5.0 L/min (range of 48.3-58.3 L/min), and % predicted FEV1 of 35 ± 11% (range of 24-46%), which clearly overlaps the ranges recited in instant claims 2, 15 and 28 (i.e., < 45-55 L/min) and instant claims 3, 16 and 29 (i.e., < 36-44%). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) …" [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

Also, as the '565 claims clearly provide for the nebulized aqueous solution of revefenacin to exhibit a pH of between 3-8, such range clearly circumscribes Applicant's instantly claimed pH ranges of "about 4.5 to about 5.5" (claim 31) and "about 4.8 to about 5.2" (claim 32), thereby rendering such ranges *prima facie* obvious. MPEP §2144.05.

Additionally, as the '565 claims clearly provide for the nebulized aqueous solution to contain about 0.05 μg/mL to about 10 mg/mL revefenacin, such dosage range clearly circumscribes Applicant's instantly claimed ranges or amounts of "about 20 μg/mL to about 60 μg/mL" (claim 36), "about 88 μg/3 mL" (equivalent to 29.33 μg/mL) (claim 37), or "about 175 μg/3 mL" (equivalent to 58.3 μg/mL) (claim 38), thereby rendering such ranges and/or amounts *prima facie* obvious. MPEP §2144.05.

This is a provisional nonstatutory double patenting rejection.

10. Claims 1-8, 14-21, 27-30 and 39 are rejected on the ground of nonstatutory double patenting as being unpatentable over claim 6 of U.S. Patent No. 8,912,334 B2 in view of Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS).

'334 recites a method of treating COPD comprising administering to a patient a therapeutically effective amount of revefenacin.

'334 differs from the instant claims only insofar as it does not explicitly teach administration of the revefenacin via nebulizer for treating COPD in a patient having a PIFR of < about 60 L/min and % predicted FEV1 of < about 50% (claims 1, 14, 27), PIFR of < about 50 L/min (claims 2, 15, 28), % predicted FEV1 of < about 40% (claims 3, 16, 29), or PIFR of about 20 L/min to < about 60 L/min and % predicted FEV1 of about 20% to < about 50% (claims 4, 17, 30).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[8] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2,

[8] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of <

p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have found it *prima facie* obvious to select the patient in need of treatment for COPD of the '334 claims with revefenacin via nebulizer using PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler et al. teaches that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11%) exhibited greater benefit from nebulized bronchodilator therapy – as compared to conventional DPI therapy – because patients with suboptimal PIFR of < 60 L/min were generally not capable of completely inhaling dry powder bronchodilator into the lower respiratory tract and nebulized bronchodilator therapy was able to achieve deeper penetration into the lower respiratory tract without having to rely on deep, hard inhalation to overcome the internal resistance of a DPI to deaggregate the powder into fine particles.

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about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

Applicant should note that Mahler clearly suggests the selection of COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) (or about 20 L/min to < about 60 L/min, as in claims 4, 17, and 30) and % predicted FEV1 of < about 50% (35 ± 11) (or about 20% to < about 50%, as in claims 4, 17 and 30) with nebulized bronchodilator therapy, thereby meeting the limitations of claims 1, 4, 14, 17, 27 and 30.

Regarding claims 2-3, 15-16 and 28-29:

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50 L/min in claims 2, 15 and 28 constitutes a range of < 45-55 L/min, and < about 40% in claims 3, 16 and 29 constitutes a range of < 36-44%.

The teachings of Mahler et al. suggest the selection of COPD patients for nebulizer therapy with a PIFR of 53.3 ± 5.0 L/min (range of 48.3-58.3 L/min), and % predicted FEV1 of 35 ± 11% (range of 24-46%), which clearly overlaps the ranges recited in instant claims 2, 15 and 28 (i.e., < 45-55 L/min) and instant claims 3, 16 and 29 (i.e., < 36-44%). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) …" [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

This is a non-provisional nonstatutory double patenting rejection.

11. Claims 1-8, 14-21 and 27-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 5 and 16 of U.S. Patent No. 10,106,503 B2 in view of Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS).

'503 recites a method of treating COPD in a mammal comprising administering to the mammal a pharmaceutical composition comprising revefenacin (or pharmaceutically acceptable salt thereof) and a

pharmaceutically acceptable carrier, wherein the composition is administered in an amount sufficient to provide about 10 μg/day to about 200 μg/day of revefenacin (or pharmaceutically acceptable salt thereof), and further wherein the composition is administered using nebulizer inhaler (patent claims 5, 16).

'503 differs from the instant claims only insofar as it does not explicitly teach administration of the nebulized revefenacin for treating COPD in a patient having a PIFR of < about 60 L/min and % predicted FEV1 of < about 50% (claims 1, 14, 27), PIFR of < about 50 L/min (claims 2, 15, 28), % predicted FEV1 of < about 40% (claims 3, 16, 29), or PIFR of about 20 L/min to < about 60 L/min and % predicted FEV1 of about 20% to < about 50% (claims 4, 17, 30).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[9] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2, p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be

[9] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have found it *prima facie* obvious to select the patient in need of treatment for COPD with the nebulized composition of revefenacin of the '503 claims by PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler et al. teaches that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11%) exhibited greater benefit from nebulized bronchodilator therapy – as compared to conventional DPI therapy – because patients with suboptimal PIFR of < 60 L/min were generally not capable of completely inhaling dry powder bronchodilator into the lower respiratory tract and nebulized bronchodilator therapy was able to achieve deeper penetration into the lower respiratory tract without having to rely on deep, hard inhalation to overcome the internal resistance of a DPI to deaggregate the powder into fine particles.

Applicant should note that Mahler clearly suggests the selection of COPD patients with PIFR of < 60 L/min (53.3 ± 5.0 L/min) (or about 20 L/min to < about 60 L/min, as in claims 4, 17, and 30) and % predicted FEV1 of < about 50% (35 ± 11) (or about 20% to < about 50%, as in claims 4, 17 and 30) with nebulized bronchodilator therapy, thereby meeting the limitations of claims 1, 4, 14, 17, 27 and 30.

Regarding claims 2-3, 15-16 and 28-29:

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50 L/min in claims 2, 15 and 28 constitutes a range of < 45-55 L/min, and < about 40% in claims 3, 16 and 29 constitutes a range of < 36-44%.

The teachings of Mahler et al. suggest the selection of COPD patients with a PIFR of 53.3 ± 5.0 L/min (range of 48.3-58.3 L/min), and % predicted FEV1 of 35 ± 11% (range of 24-46%), which clearly overlaps the ranges recited in instant claims 2, 15 and 28 (i.e., < 45-55 L/min) and instant claims 3, 16 and 29 (i.e., < 36-44%). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) …" [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient

to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

This is a non-provisional nonstatutory double patenting rejection.

12. Claims 1-8, 14-21 and 27-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 3 and 14 of U.S. Patent No. 10,334,995 B2 in view of Gerhart et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016) and Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS),

citing to Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS) as evidence.

'995 recites a method of producing bronchodilation in a mammal or human patient comprising administering to the mammal or human patient a pharmaceutical composition comprising revefenacin (or pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, wherein the composition is administered in an amount sufficient to provide about 10 μg/day to about 200 μg/day of revefenacin (or pharmaceutically acceptable salt thereof), and further wherein the composition is administered using nebulizer inhaler (patent claims 3, 14).

'995 differs from the instant claims only insofar as it does not explicitly teach administration of the nebulized revefenacin for treating COPD in a patient having a PIFR of < about 60 L/min and % predicted FEV1 of < about 50% (claims 1, 14, 27), PIFR of < about 50 L/min (claims 2, 15, 28), % predicted FEV1 of < about 40% (claims 3, 16, 29), or PIFR of about 20 L/min to < about 60 L/min and % predicted FEV1 of about 20% to < about 50% (claims 4, 17, 30).

Gerhart et al. teaches that there are two general categories of bronchodilator therapy for the treatment of COPD, which are (i) muscarinic antagonists, and (ii) β-adrenergic receptor agonists (p.1, para.[0006]). Gerhart et al. teaches that muscarinic antagonists are generally preferred and recommended as first-line therapy for maintenance treatment of moderate to severe COPD (p.1, para.[0006]). Gerhart et al. teaches that muscarinic antagonists are either long-acting or short-acting, with long-acting muscarinic antagonists being preferred to short-acting as a result of their superior efficacy and duration of effect (p.1, para.[0006]). Gerhart et al. teaches long-acting muscarinic antagonists with therapeutic effect lasting more than about 6 hours, including TD-4208 (p.6, para.[0047]).

Quinn et al. is cited as factual evidence that TD-4208 is synonymous with revefenacin (abstract).

Mahler et al. teaches an experimental study of 20 COPD patients with PIFR[10] of < 60 L/min (53.3 ± 5.0 L/min) and % predicted FEV1 of 35 ± 11 (abstract; "Study Subjects", col.1, para.3, p.104; Table 2, p.106). Mahler et al. teaches that the experimental study compared the efficacy of arformoterol aerosol solution (15 μg/2 mL) via nebulizer with salmeterol dry powder (50 μg) administered via DISKUS inhaler, and observed that at 15 min following administration, improvements in FEV1, FVC and IC were significantly higher with nebulized arformoterol than with dry powder salmeterol, and that at 2 hr following administration, changes in FVC and IC, but not FEV1, were significantly higher with nebulized arformoterol than with dry powder salmeterol (abstract; col.2, para.2, p.105-col.2, para.2, p.106; Table 3, p.106). Mahler et al. teaches that, at peak effect (2 hr), volume responses were greater with arformoterol via nebulizer compared with dry powder salmeterol in COPD patients with PIFR of < 60 L/min (abstract). Mahler et al. teaches that patients with suboptimal PIFR may not be capable of completely inhaling a dry powder bronchodilator into their lower respiratory tract (as a deep, hard inhalation is required to overcome the internal resistance of a DPI to deaggregate the powder into fine particles) and suggests that nebulized aerosol arformoterol achieved deeper penetration into the lower respiratory tract (col.1, para.1, p.107-col.2, para.1, p.107). Mahler et al. teaches that bronchodilator therapy via nebulization should be

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[10] At col.2, para.1, p.104, Mahler et al. teaches that PIFR was measured using the IN-CHECK DIAL device using the simulated internal resistance of the DISKUS dry powder inhaler, which meets Applicant's definition set forth at p.5, l.18-24 of the as-filed specification, which defines the PIFR of < about 60 L/min as being measured "against the simulated resistance of a DISKUS® device". See also p.11, l.6-20 of the as-filed specification.

considered in COPD patients with suboptimal PIFR against a particular DPI (abstract; col.1, para.3, p.108).

A person of ordinary skill in the art before the effective filing date of the claimed invention would have had a reasonable expectation of success in administering the nebulized revefenacin of the '995 claims for treating COPD via bronchodilation in a patient in need thereof because Gerhart et al. teaches revefenacin as a muscarinic antagonist bronchodilator for the treatment of COPD. The skilled artisan would have been motivated to administer the nebulized revefenacin of the '995 claims for treating COPD via bronchodilation in a patient in need thereof because Gerhart et al. teaches muscarinic antagonists as preferred first-line bronchodilator therapy for maintenance treatment of moderate to severe COPD, and further teaches revefenacin as a long-acting muscarinic antagonist with therapeutic bronchodilating effect lasting more than about 6 hours. It would, therefore, have been *prima facie* obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to modify the '995 claims to administer the nebulized revefenacin for the treatment of COPD via bronchodilation in a patient in need thereof in view of revefenacin's established therapeutic efficacy as a long-acting muscarinic antagonist bronchodilator effective for the treatment of moderate to severe COPD, as evidenced by Gerhart et al.

The ordinarily skilled artisan would have also found it *prima facie* obvious to select the patient in need of treatment for COPD with the nebulized bronchodilator revefenacin by PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler et al. teaches that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 $\pm$ 5.0 L/min) and % predicted FEV1 of < about 50% (35 $\pm$ 11%) exhibited greater benefit from nebulized bronchodilator therapy – as compared to DPI therapy – because patients with suboptimal PIFR of < 60 L/min were generally not capable of completely inhaling dry powder bronchodilator into the lower respiratory tract and nebulized bronchodilator therapy was able to achieve deeper penetration into the lower respiratory tract without having to rely on deep, hard inhalation to overcome the internal resistance of a DPI to deaggregate the powder into fine particles.

Applicant should note that Mahler clearly suggests the selection of COPD patients with PIFR of < 60 L/min (53.3 $\pm$ 5.0 L/min) (or about 20 L/min to < about 60 L/min, as in claims 4, 17, and 30) and %

predicted FEV1 of < about 50% (35 ± 11) (or about 20% to < about 50%, as in claims 4, 17 and 30) with nebulized bronchodilator therapy, thereby meeting the limitations of claims 1, 4, 14, 17, 27 and 30.

Regarding claims 2-3, 15-16 and 28-29:

At p.5, l.11 of the as-filed specification, Applicant defines the term "about" as ± 10% of the recited value. As a result, Applicant's recitation of < about 50 L/min in claims 2, 15 and 28 constitutes a range of < 45-55 L/min, and < about 40% in claims 3, 16 and 29 constitutes a range of < 36-44%.

The teachings of Mahler et al. suggest the selection of COPD patients with a PIFR of 53.3 ± 5.0 L/min (range of 48.3-58.3 L/min), and % predicted FEV1 of 35 ± 11% (range of 24-46%), which clearly overlaps the ranges recited in instant claims 2, 15 and 28 (i.e., < 45-55 L/min) and instant claims 3, 16 and 29 (i.e., < 36-44%). MPEP §2144.05 states, "In the case wherein the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990) …" [A] prior art reference that discloses a range encompassing a somewhat narrower range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005)."

This is a non-provisional nonstatutory double patenting rejection.

Conclusion

Rejection of claims 1-8, 14-21 and 27-53 is proper.
Claims 9-13 and 22-26 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).
No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is reminded that MPEP §2001.06(b) clearly states that "[t]he individuals covered by 37 C.F.R. 1.56 have a duty to bring to the attention of the examiner, or other Office official involved with the

examination of a particular application, information within their knowledge as to other copending United States applications which are "material to patentability" of the application in question." See *Armour & Co. v. Swift & Co.*, 466 F.2d 767, 779, 175 USPQ 70, 79 (7th Cir. 1972). MPEP §2001.06(b) clearly indicates that "if a particular inventor has different applications pending in which similar subject matter but patentably indistinct claims are present that fact must be disclosed to the examiner of each of the involved applications." See *Dayco Prod. Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1365-69, 66 USPQ2d 1801, 1806-08 (Fed. Cir. 2003).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached on Monday through Friday (08:30 AM to 05:00 PM).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

July 3, 2021

PATENT
Attorney Docket No. P-340-US1
Customer No. 27038

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
BARNES et al.	)	Confirmation No.: 8316
	)	
Application No.: 16/555,216	)	Group Art Unit: 1629
	)	
Filed: August 29, 2019	)	Examiner: Leslie A. Royds Draper
	)	
For: METHODS FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE	)	

RESPONSE PURSUANT TO 37 C.F.R. §1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This reply is being filed in response to the Office Action dated July 8, 2021, in the above-identified patent application. The Office Action set a three-month period for response and therefore, this reply is due on or before October 8, 2021. In response to the Office Action, entry of the following amendments and consideration of the following remarks is respectfully requested.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in this application.

1-26. (Canceled)

27. (Currently Amended) A method for treating chronic obstructive pulmonary disease in a patient, the method comprising:

(a) selecting a patient having chronic obstructive pulmonary disease for treatment based on the patient having a peak inspiratory flow rate less than about 60 L/min and a percent predicted force expiratory volume in one second less than about 50 percent; and

(b) administering a pharmaceutical composition comprising an aqueous solution of revefenacin or a pharmaceutically acceptable salt thereof to the selected patient using a nebulizer.

28. (Original) The method of Claim 27, wherein the patient has a peak inspiratory flow rate less than about 50 L/min.

29. (Original) The method of Claim 27, wherein the patient has a percent predicted force expiratory volume in one second less than about 40 percent.

30. (Original) The method of Claim 27, wherein the patient has a peak inspiratory flow rate in the range of about 20 L/min to less than about 60 L/min and a percent predicted force expiratory volume in one second in the range of from about 20 percent to less than about 50 percent.

31. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition has a pH in the range of about 4.5 to about 5.5.

32. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition has a pH of about 4.8 to about 5.2.

33. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition is isotonic.

34. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition further comprises sodium chloride, citric acid and sodium citrate.

35. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition is sterile, isotonic and has a pH of about 4.8 to about 5.2.

36. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition comprises about 20 µg/mL to about 60 µg/mL of revefenacin or a pharmaceutically acceptable salt thereof.

37. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition comprises about 88 µg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof.

38. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition comprises about 175 µg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof.

39. (Original) The method of any one of Claims 27 to 30, wherein the pharmaceutical composition is administered using a jet nebulizer.

40-53. (Canceled)

REMARKS

Applicants respectfully request reconsideration of this application in view of the above amendments and following remarks.

1. Status of the Claims

Claims 1-53 were previously pending in this application. Claims 1-26 and 40-53 are being canceled in this paper. Accordingly, Claims 27-39 are now pending.

2. Summary of the Amendments

Claims 1-26 and 40-53 have been canceled without prejudice or disclaimer.

Claim 27 has been amended to specify that the patient in step (a) has chronic obstructive pulmonary disease. Support for this amendment is found, e.g., on page 12, lines 05-10.

Entry of these amendments is respectfully requested.

3. Information Disclosure Statements

The Office Action indicates that two documents submitted with the November 25, 2019 Information Disclosure Statement (including Form PTO/SB/08A)(the "IDS") have not been considered because the IDS did not identify the date of publication, publisher, author (if any), relevant pages of the publication and place of publication for these citations (specifically, items 1 and 11 in the Non-Patent Literature Citations). Applicants are resubmitting these two documents in an IDS with additional identifying information.

4. Rejections Under 35 U.S.C. §101

Claims 40-53 have been rejected under 35 U.S.C. §101 because the claimed invention is allegedly directed to a judicial exception as explained in the Office Action. While not agreeing with this rejection, Claims 40-53 have been canceled and therefore, this rejection is now moot. Accordingly, the rejection of Claims 40-53 under 35 U.S.C. §101 can be withdrawn.

5. Rejections Under 35 U.S.C. §112(b)

Claims 1-8, 14-21 and 27-39 have been rejected under 35 U.S.C. §112(b) or 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter the inventors regard as the invention.

More specifically, the Office Action indicates that Claim 27 recites a method for treating COPD in a patient, but it is allegedly not clear whether the patient specified in step (a) of the method is in need of treatment for COPD, or whether it could be any patient. In response, Applicants have amended Claim 27 to specify that the patient in step (a) has chronic obstructive pulmonary disease. Accordingly, this rejection (and the related rejections of dependent claims 28-39) can be withdrawn.

Claims 1-8 and 14-21 have also been rejected under 35 U.S.C. §112(b) or 35 U.S.C. §112, second paragraph. While not agreeing with these rejections, Claims 1-8 and 14-21 have been canceled and therefore, these rejections are now moot.

Accordingly, for the forgoing reasons, the rejections of Claims 1-8, 14-21 and 27-39 under 35 U.S.C. §112(b) or 35 U.S.C. §112, second paragraph, can be withdrawn.

6. Rejections Under 35 U.S.C. §102

Claims 1, 4, 5, 17, 18, 40, 43, 44, 47, 50 and 51 have been rejected under 35 U.S.C. §102(a)(1) as allegedly being anticipated by Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109.

While not agreeing with this rejection, Claims 1, 4, 5, 17, 18, 40, 43, 44, 47, 50 and 51 have been canceled and therefore, this rejection is now moot. Accordingly, the rejection of Claims 1, 4, 5, 17, 18, 40, 43, 44, 47, 50 and 51 under 35 U.S.C. §102(a)(1) can be withdrawn.

7. Rejections Under 35 U.S.C. §103

Claims 2, 3, 15, 16, 41, 42, 48 and 49 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109. Claims 6-8, 19-21, 45, 46, 52 and 53 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109; in view of Gerhart et al., U.S.

Patent Application Publication No. 2016/0166506, citing Quinn et al., *Pulmonary Pharmacology & Therapeutics*, 2018, 48:71-79 (Published Online October 4, 2017). While not agreeing with these rejections, Claims 2, 3, 6-8, 15, 16, 19-21, 41, 42, 45, 46, 48, 49, 52 and 53 have been canceled and therefore, these rejections are now moot.

Claims 27-34 and 39 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109; in view of Quinn et al., *Pulmonary Pharmacology & Therapeutics*, 2018, 48:71-79 (Published Online October 4, 2017).

The present invention is based, in part, on the discovery that patients having both low peak inspiratory flow rate (PIFR) and low percent predicted FEV_1 (<50 %) achieved significantly greater improvements in trough FEV_1 and trough forced vital capacity (FVC) when a bronchodilator (revefenacin) was administered using a nebulizer compared to a bronchodilator (tiotropium) delivered using a dry powder inhaler. In contrast, in patients having low PIFR but a percent predicted $FEV_1 \geq 50$ %, a significant difference in trough FEV_1 and FVC was not observed between patients using a nebulizer versus patients using a dry powder inhaler. Thus, it has now been discovered that COPD patients having low PIFR and a percent predicted FEV_1 <50 % will gain additional benefit from a bronchodilator if the bronchodilator is delivered to such patients using a nebulizer instead of a dry powder inhaler. This unexpected discovery can be used to treat COPD patients with a nebulized bronchodilator, such as revefenacin, thereby improving the therapeutic outcome for such patients.

As amended, the presently claimed method for treating COPD in a patient comprises the steps of (a) selecting a patient having chronic obstructive pulmonary disease for treatment based on the patient having a peak inspiratory flow rate less than about 60 L/min and a percent predicted force expiratory volume in one second less than about 50 percent; and (b) administering a pharmaceutical composition comprising an aqueous solution of revefenacin or a pharmaceutically acceptable salt thereof to the selected patient using a nebulizer.

Mahler teaches that a PIFRresist of < 60 L/min may be a useful criterion for determining when to use a nebulizer to deliver bronchodilator medications versus a dry powder inhaler. For example:

> Our study is the first to prospectively examine whether using a threshold of PIFRresist of < 60 L/min against a specific DPI is a useful criterion for when to use a nebulizer to deliver bronchodilator medications. Mahler at page 108, left column.

Mahler's study examined arfomoterol (a bronchodilator) delivered via a nebulizer compared with dry powder salmeterol (a bronchodilator) in 20 patients with COPD who had a PIFRresist of < 60 L/min. Mahler recognized that their study was insufficient to definitively answer the question of when nebulized bronchodilator therapy should be prescribed for patients with COPD. For example:

> Our results should be interpreted with caution until supported by a prospective and double-blind study with a larger number of patients. A 1-2 week randomized controlled trial comparing dry powder and nebulized bronchodilators is needed in patients with COPD who exhibit a suboptimal PIFRresist to further address the question, "When should nebulized bronchodilator therapy be prescribed for patients with COPD?" Mahler at page 108, left column.

Quinn describes two randomized, double-blind, phase 2 studies of revefenacin in patients with COPD to provide an initial assessment of efficacy and safety in the relevant patient population, and to inform dose selection for subsequent phase 2 and 3 clinical studies (Quinn at page 72, left column).

Neither Mahler nor Quinn, alone or when combined, teach or suggest the presently claimed invention. Mahler does not teach or suggest that COPD patients should be selected for treatment based on both low PIFR and low percent predicted FEV_1. Instead, Mahler only selects patients based on low PIFR. Nowhere in Mahler does it teach or suggest that Mahler selected patients based on percent predicted FEV_1 or that Mahler considered but rejected patients having a percent predicted $FEV_1 \geq 50$ %. The average percent predicted FEV_1 for the patients in the Mahler study happened to be <50%, but the patients weren't selected based on their percent predicted FEV_1. Accordingly, Mahler clearly does not teach or suggest the present invention.

Quinn does not cure this deficiency. In fact, the patients in Quinn had an FEV_1 of 35-80% of the predicted normal value (see Quinn at page 72, right column). Thus, Quinn clearly does not teach or suggest the present invention.

Moreover, even if Mahler and Quinn were deemed to somehow suggest the present invention, there is clearly no reasonable expectation of success based on the teachings of Mahler. A reasonable expectation of success must be established when modifying or combining the prior art to make a *prima facie* obviousness rejection. See MPEP §2143.02 ("Where there is a reason to modify or combine the prior art to achieve the claimed invention, the claims may only be rejected as *prima facie* obvious if there is also a reasonable expectation of success" (citing *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). The Examiner bears the burden of establishing a *prima facie* case of obviousness and this includes the burden of establishing a reasonable expectation of success. Accordingly, the Examiner cannot maintain the present rejection under 35 U.S.C. §103 without adequately establishing a reasonable expectation of success.

Mahler explicitly states that their results should be viewed "with caution" until supported by a prospective and double-blind study with a larger number of patients and that a further study is needed to understand which COPD patients will benefit most from a nebulized bronchodilator (Mahler at page 108, left column). Clearly, a person having ordinary skill in the art would not have had a reasonable expectation of success for the presently claimed invention based on the explicit cautions and caveats in Mahler. Without an adequate explanation to overcome these clear teachings in Mahler regarding a reasonable expectation of success, the present rejection under 35 U.S.C. §103 should be withdrawn.

Accordingly, for the foregoing reasons, the rejection of Claims 27-34 and 39 under 35 U.S.C. §103 over by Mahler in view of Quinn should be withdrawn.

Claim 35 has been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Mahler in view of Quinn, and further in view of U.S. Patent Application Publication No. 2004/0045546 A1 to Hirsh et al. Claim 35 further limits Claims 27-30 by specifying that the pharmaceutical composition is sterile, isotonic and has a pH of about 4.8 to about 5.2. Hirsh has been cited, in part, for its teachings related to sterile, isotonic saline solutions. However, Hirsh does not teach or suggest the invention as a whole claimed in Claim 27 nor does it cure the deficiencies of Mahler and Quinn discussed above. Accordingly, for the foregoing reasons, the rejection of Claim 35 under 35 U.S.C. §103 over by Mahler in view of Quinn, and further in view of Hirsh should be withdrawn.

Claims 36-38 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Mahler in view of Quinn, and further in view of Pudi et al., *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017). Claims 36-38 further limit Claims 27-30 by specifying that pharmaceutical composition comprises about 20 µg/mL to about 60 µg/mL of revefenacin or a pharmaceutically acceptable salt thereof; about 88 µg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof; or about 175 µg/3 mL of revefenacin or a pharmaceutically acceptable salt thereof. Pudi has been cited, in part, for its teachings related to the amounts of revefenacin or a pharmaceutically acceptable salt thereof found in pharmaceutical compositions. However, Pudi does not teach or suggest the invention as a whole claimed in Claim 27 nor does it cure the deficiencies of Mahler and Quinn discussed above. Accordingly, for the foregoing reasons, the rejection of Claim 36-38 under 35 U.S.C. §103 over by Mahler in view of Quinn, and further in view of Pudi should be withdrawn.

Accordingly, for the foregoing reasons, the rejections of Claims 27-39 under 35 U.S.C. §103 should be withdrawn.

8. Non-Statutory Obviousness-Type Double Patenting Rejections

Claims 1-8, 14-21, 27-32 and 36-39 have been provisionally rejected under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claims 27-30, 35 and 36 of U.S. Patent Application No. 16/744,565 in view of U.S. Patent Application Publication No. 2016/0166506 A1 to Gerhart et al. and Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109; citing to Quinn et al., *Pulmonary Pharmacology & Therapeutics*, 2018, 48:71-79 (Published Online October 4, 2017).

First, Applicants note that Claims 1-8 and 14-21 have been canceled so this provisional rejection is moot for those claims.

Claims 27-30, 35 and 36 of U.S. Patent Application No. 16/744,565 relate to a nebulizer inhaler comprising a pharmaceutical composition comprising a pharmaceutically-acceptable aqueous carrier and revefenacin or a pharmaceutically acceptable salt thereof. The pending claims of the '565 application do not teach or suggest the presently claimed method of Claim 27-32 and 36-39 for treating COPD patients that includes the step of selecting a patient for treatment based on both low PIFR and low percent predicted FEV_1.

Gerhart, Mahler and Quinn do not cure this deficiency. Gerhart is concerned, in part, with a method for improving lung function in COPD patients by administering a muscarinic antagonist with a high efficiency nebulizer. Gerhart does not teach or suggest selecting COPD patients for treatment having a peak inspiratory flow rate less than about 60 L/min and a percent predicted force expiratory volume in one second less than about 50 percent. And as noted herein, neither do Mahler or Quinn. Accordingly, the provisional rejection of Claims 1-8, 14-21, 27-32 and 36-39 under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claims 27-30, 35 and 36 of U.S. Patent Application No. 16/744,565 in view of Gerhart and Mahler, citing Quinn, should be withdrawn.

Claims 1-8, 14-21, 27-30 and 39 have been rejected under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claim 6 of U.S. Patent No. 8,912,334 in view of Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109; citing to Quinn et al., *Pulmonary Pharmacology & Therapeutics*, 2018, 48:71-79 (Published Online October 4, 2017).

First, Applicants note that Claims 1-8 and 14-21 have been canceled so this rejection is moot for those claims.

Claim 6 of U.S. Patent No. 8,912,334 teaches a method of treating COPD or asthma comprising administering to a patient a therapeutically effective amount of revefenacin or a pharmaceutically acceptable salt or stereoisomer thereof. U.S. Patent No. 8,912,334 does not teach or suggest selecting COPD patients for treatment having a peak inspiratory flow rate less than about 60 L/min and a percent predicted force expiratory volume in one second less than about 50 percent. For the reasons noted herein, neither do Mahler or Quinn. Accordingly, the rejection of Claims 1-8, 14-21, 27-30 and 39 under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claim 6 of U.S. Patent No. 8,912,334 in view of Mahler, citing to Quinn, should be withdrawn.

Claims 1-8, 14-21 and 27-30 have been rejected under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claims 5 and 16 of U.S. Patent No. 10,106,503 in view of Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109.

First, Applicants note that Claims 1-8 and 14-21 have been canceled so this rejection is moot for those claims.

Claims 5 and 16 of U.S. Patent No. 10,106,503 teaches methods of treating COPD and asthma, or COPD, in a mammal comprising administering to the mammal using a nebulizer inhaler a pharmaceutical composition comprising a pharmaceutically acceptable carrier and revefenacin or a pharmaceutically acceptable salt thereof; wherein the pharmaceutical composition is administered to the mammal in an amount sufficient to provide about 10 µg/day to about 200 µg/day of revefenacin or a pharmaceutically acceptable salt thereof. U.S. Patent No. 10,106,503 does not teach or suggest selecting COPD patients for treatment having a peak inspiratory flow rate less than about 60 L/min and a percent predicted force expiratory volume in one second less than about 50 percent. For the reasons noted herein, neither does Mahler. Accordingly, the rejection of Claims 1-8, 14-21 and 27-30 under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claim 5 and 16 of U.S. Patent No. 10,106,503 in view of Mahler should be withdrawn.

Claims 1-8, 14-21 and 27-30 have been rejected under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claims 3 and 14 of U.S. Patent No. 10,334,995 in view of U.S. Patent Application Publication No. 2016/0166506 A1 to Gerhart et al. and Mahler et al., *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2): 103-109; citing to Quinn et al., *Pulmonary Pharmacology & Therapeutics*, 2018, 48:71-79 (Published Online October 4, 2017).

First, Applicants note that Claims 1-8 and 14-21 have been canceled so this rejection is moot for those claims.

Claims 3 and 14 of U.S. Patent No. 10,334,995 teaches methods producing bronchodilation in a mammal or a human comprising administering to the mammal or human using a nebulizer inhaler a pharmaceutical composition comprising a pharmaceutically acceptable carrier and revefenacin or a pharmaceutically acceptable salt thereof; wherein the pharmaceutical composition is administered to the mammal in an amount sufficient to provide about 10 µg/day to about 200 µg/day of revefenacin or a pharmaceutically acceptable salt thereof. U.S. Patent No. 10,334,995 does not teach or suggest selecting COPD patients for treatment having a peak inspiratory flow rate less than about 60 L/min and a percent predicted

force expiratory volume in one second less than about 50 percent. For the reasons noted herein, neither do Gerhart, Mahler or Quinn. Accordingly, the rejection of Claims 1-8, 14-21 and 27-30 under the judicially-created doctrine of non-statutory obviousness-type double patenting as being unpatentable over Claim 3 and 14 of U.S. Patent No. 10,334,995 in view of Gerhart and Mahler, citing to Quinn, should be withdrawn.

For the foregoing reasons, each of the above non-statutory obviousness-type double patenting rejections can be withdrawn.

Should there be any questions regarding this paper or this application, the Examiner is encouraged to telephone the undersigned attorney for Applicants at (650) 808-6406.

Respectfully submitted,

Date: September 17, 2021

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/555,216	08/29/2019	CHRISTOPHER NOEL BARNES	P-340-US1	8316

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EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
12/29/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SheppardMullin_Pair@firsttofile.com
patent@theravance.com
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Office Action Summary	Application No. 16/555,216	Applicant(s) BARNES et al.	
	Examiner Leslie A Royds Draper	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 17 September 2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 27-39 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 27-39 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 17Sept21.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 27-39 are presented for examination.

Applicant's Amendment filed September 17, 2021 has been entered into the present application. Claims 27-39 remain pending. Claim 27 is amended. Claims 1-26 and 40-53 are cancelled.

Applicant's arguments, filed September 17, 2021, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Requirement for Restriction/Election

Applicant is reminded of his election without traverse of (i) a muscarinic antagonist as the single disclosed species of bronchodilator, and (ii) revefenacin as the single disclosed species of muscarinic antagonist, as stated in the reply filed March 18, 2021, which is still in effect over the claims.

Instant claims 27-39 remain drawn to the elected species and such claims are herein acted on the merits *infra*.

Status of Rejections Set Forth in the July 8, 2021 Non-Final Office Action

In reply to the rejection of claims 40-53 under 35 U.S.C. §101 for patent ineligible subject matter, as set forth at p.4-9 of the previous Office Action dated July 8, 2021, Applicant now cancels claims 40-53. Accordingly, the rejection is now hereby withdrawn.

In reply to the rejection of claims 1-8, 14-21 and 27-39 under 35 U.S.C. §112(b) (pre-AIA second paragraph), as set forth at p.10-11 of the previous Office Action dated July 8, 2021, Applicant now cancels claims 1-8 and 14-21, and further amends claim 27 to specifically recite in step (a) that the selection is of "a patient having chronic obstructive pulmonary disease [COPD] for treatment based on the patient" exhibiting the recited peak inspiratory flow rate (PIFR) of < about 60 L/min and a percent

predicted force expiratory volume in one second (% predicted FEV1) of < about 50%, thereby clarifying that the patient of the recited method must have COPD. Accordingly, the rejection is now hereby withdrawn.

In reply to the rejection of claims 1, 4-5, 14, 17-18, 40, 43-44, 47 and 50-51 under 35 U.S.C. §102(a)(1) as being anticipated by Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS), as set forth at p.11-15 of the previous Office Action dated July 8, 2021, Applicant now cancels claims 1, 4-5, 14, 17-18, 40, 43-44, 47 and 50-51. Accordingly, the rejection is now hereby withdrawn.

In reply to the rejection of claims 2-3, 15-16, 41-42 and 48-49 under 35 U.S.C. §103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS), as set forth at p.15-17 of the previous Office Action dated July 8, 2021, Applicant now cancels claims 2-3, 15-16, 41-42 and 48-49. Accordingly, the rejection is now hereby withdrawn.

In reply to the rejection of claims 6-8, 19-21, 45-46 and 52-53 under 35 U.S.C. §103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Gerhart et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016), citing to Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS), as set forth at p.17-21 of the previous Office Action dated July 8, 2021, Applicant now cancels claims 6-8, 19-21, 45-46 and 52-53. Accordingly, the rejection is now hereby withdrawn.

Information Disclosure Statement

Applicant's Information Disclosure Statement filed September 17, 2021 (two pages total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08A, the Examiner has considered the cited references.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

1. Claims 27-34 and 39 are rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic

Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS), each already of record, for the reasons of record set forth at p.21-25 of the previous Office Action dated July 8, 2021, of which said reasons are herein incorporated by reference.

Newly amended claim 27 now clarifies that the patient in step (a) of the recited method has COPD and is selected for treatment based upon a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%. As the teachings of Mahler et al. are clearly directed to the selection of 20 COPD study subjects with PIFR of < 60 L/min (53.3 $\pm$ 5.0 L/min) and % predicted FEV1 of < 50% (35 $\pm$ 11), such teachings as set forth in the rejection continue to meet Applicant's claims as amended.

Response to Applicant's Arguments

In reply, Applicant traverses the rejection, stating that "Mahler does not teach or suggest that COPD patients should be selected for treatment based on both low PIFR and low percent predicted FEV1", alleging that "Mahler only selected patients based on low PIFR" and that "[t]he average percent predicted FEV1 for the patients in the Mahler study happened to be <50%, but the patients weren't selected based on their percent predicted FEV1" (Remarks, p.7).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant's position is not understood. In the instant case, Mahler et al. clearly discloses the selection of 20 COPD subjects exhibiting PIFR of < 60 L/min (specifically, 53.3 $\pm$ 5.0 L/min) and also exhibiting % predicted FEV1 of < about 50% (specifically, 35 $\pm$ 11 %). Though Applicant may take the position that the main selection criteria of Mahler's experimental study was PIFR value of < 60 L/min and not % predicted FEV1 of < 50%, the fact remains that Mahler specifically selected 20 COPD subjects – out of the population of possible COPD subjects - for treatment with PIFR of < 60 L/min that also exhibited a % predicted FEV1 of < 50%. This meets the requirements of Applicant's defined "selection" step of part (a) of instant claim 27. It is immaterial as to whether such selection criteria was actively or passively considered – the material question is whether the selection of such COPD subjects yielded a

population that exhibited the recited characteristics of PIFR (< 60 L/min) and % predicted FEV1 (< 50%). This is clearly taught by Mahler's teachings and, therefore, constitutes a relevant teaching of the same.

Applicant goes on to argue that "Quinn does not cure this deficiency", noting that "the patients in Quinn had an FEV1 of 35-80% of the predicted normal value", asserting that "Quinn clearly does not teach or suggest the present invention" (Remarks, p.7).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant fails to consider what Quinn et al. was relied upon to actually teach. Here, Quinn et al. was cited for its teachings of the long-acting muscarinic antagonist revefenacin as effective bronchodilator therapy with rapid onset and sustained duration when administered via jet nebulizer to patients with moderate to severe COPD, particularly when administered in doses of 22, 44, 88, 175, 350 and 700 μg in 10 mM citrate buffer in normal saline at pH 5.0. A person of ordinary skill in the art, therefore, would have found it *prima facie* obvious to substitute Quinn's nebulized revefenacin bronchodilator therapy for Mahler's nebulized arformoterol bronchodilator therapy for treating COPD subjects as claimed in view of the known efficacy of each as effective nebulized bronchodilator therapy for treating COPD. The fact that Quinn's COPD subjects exhibit a range of % predicted FEV1 values only serves to further underscore the suitability and efficacy of revefenacin bronchodilator therapy for the treatment of COPD subjects that do exhibit % predicted FEV1 values of < 50% as claimed, including those subjects of Mahler et al. Applicant is reminded that there is no requirement under 35 U.S.C. §103 that any one or more of the individual references cited in the rejection – such as Quinn alone - must teach the entirety of the claimed invention. Rather, the test for obviousness is what the combined teachings of the cited references would have suggested to the ordinarily skilled artisan. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant opines that "even if Mahler and Quinn were deemed to somehow suggest the present invention, there is clearly no reasonable expectation of success based on the teachings of Mahler" because the reference "explicitly stated that their results should be viewed 'with caution' until supported by a prospective and double-blind study with a larger number of patients and that a further study is needed to understand which COPD patients will benefit most from a nebulized bronchodilator" (Remarks, p.8).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant's position that Mahler et al. fails to provide a reasonable expectation of success is unavailing. Here, Mahler et al. clearly suggests that nebulized bronchodilator therapy should be considered in COPD patients who have a suboptimal PIFR against a dry powder inhaler (as a deep, hard inhalation is required to overcome the internal resistance of a dry powder inhaler to deaggregate the powder into fine particles), because the nebulized aerosol bronchodilator therapy achieved deeper penetration into the lower respiratory tract, and further exemplifies this effect in COPD patients with PIFR of < 60 L/min and % predicted FEV1 of < 50%. Such teachings underpin the reasonable expectation of success that is clearly borne out by the cited prior art references. Applicant is reminded that obviousness requires only a reasonable expectation of success – which is clearly supported by Mahler's proof-of-principle teachings, but not absolute predictability and guaranteed success. MPEP §2143.02(II).

For these reasons *supra*, rejection of claims 27-34 and 39 is proper.

2. Claim 35 remains rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS),

as applied above to claims 27-34 and 39,

further in view of Hirsh et al. (U.S. Patent Application Publication No. 2004/0045546 A1; 2004),

each already of record, for the reasons of record set forth at p.25-26 of the previous Office Action dated July 8, 2021, of which said reasons are herein incorporated by reference.

Response to Applicant's Arguments

In reply, Applicant traverses the rejection, stating that "Hirsh does not teach or suggest the invention as a whole claimed in [c]laim 27 nor does it cure the deficiencies of Mahler and Quinn discussed above", urging that the rejection should be withdrawn (Remarks, p.8).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant's arguments are predicated upon a finding that the combination of Mahler et al. and Quinn et al. is deficient, which it is not for the reasons set forth above (which are herein incorporated by reference). Moreover, Applicant is reminded that Hirsh was relied upon for its teachings of why one of ordinary skill in the art before the effective filing date of the claimed invention would have formulated Quinn's aqueous revefenacin solution in normal saline with sterile, isotonic saline for use in the manner suggested by Mahler as modified by Quinn. Piecemeal analysis of the references cannot establish non-obviousness because it fails to consider the totality of the teachings and what they would have reasonably suggested to the ordinarily skilled artisan when combined. Also, there is no requirement under 35 U.S.C. §103 that any one or more of the individual references – such as Hirsh alone - cited in the rejection must teach the entirety of the claimed invention. Rather, the test for obviousness is what the combined teachings of the cited references would have suggested to the ordinarily skilled artisan. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For these reasons *supra*, rejection of claim 35 is proper.

3. Claims 36-38 remain rejected under 35 U.S.C. 103 as being unpatentable over Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS) in view of Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS),

as applied above to claims 27-34 and 39,

further in view of Pudi et al. ("A 28 Day, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Nebulized Revefenacin in Patients with Chronic Obstructive Pulmonary Disease", *Respiratory Research*, 2017; 18:182, Published Online November 2, 2017),

each already of record, for the reasons of record set forth at p.26-28 of the previous Office Action dated July 8, 2021, of which said reasons are herein incorporated by reference.

Response to Applicant's Arguments

In reply, Applicant traverses the rejection, stating that "Pudi does not teach or suggest the invention as a whole claimed in [c]laim 27 nor does it cure the deficiencies of Mahler and Quinn discussed above", urging that the rejection should be withdrawn (Remarks, p.9).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant's arguments are predicated upon a finding that the combination of Mahler et al. and Quinn et al. is deficient, which it is not for the reasons set forth above (which are herein incorporated by reference). Moreover, Applicant is reminded that Pudi was relied upon for its teachings of why one of ordinary skill in the art before the effective filing date of the claimed invention would have formulated Quinn's aqueous revefenacin nebulization solution to comprise 88 μg in 3 mL or 175 μg in 3 mL for use in the manner suggested by Mahler as modified by Quinn. Piecemeal analysis of the references cannot establish non-obviousness because it fails to consider the totality of the teachings and what they would have reasonably suggested to the ordinarily skilled artisan when combined. Also, there is no requirement under 35 U.S.C. §103 that any one or more of the individual references – such as Pudi alone - cited in the rejection must teach the entirety of the claimed invention. Rather, the test for obviousness is what the combined teachings of the cited references would have suggested to the ordinarily skilled artisan. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For these reasons *supra*, rejection of claims 36-38 is proper.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

4. Claims 27-32 and 36-39 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 27-30 and 35-36 of U.S. Patent Application No. 16/744,565 in view of Gerhart et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016) and Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS),

citing to Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS) as evidence,

each already of record, for the reasons of record set forth at p.28-32 of the previous Office Action dated July 8, 2021, of which said reasons are herein incorporated by reference.

Applicant's cancellation of claims 1-8 and 14-21 necessitates the removal of such claims from the statement of the rejection above.

Newly amended claim 27 now clarifies that the patient in step (a) of the recited method has COPD and is selected for treatment based upon a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%. As the reasons for rejection are directed to the selection of COPD subjects with PIFR of < 60 L/min and % predicted FEV1 of < 50%, such teachings as set forth in the rejection continue to meet Applicant's claims as amended.

Response to Applicant's Arguments

In reply, Applicant traverses the rejection, stating that "[t]he pending claims of the '565 application do not teach or suggest the presently claimed method", further asserting that "Gerhart, Mahler and Quinn do not cure this deficiency" as none of the references "teach or suggest selecting COPD patients for treatment having a [PIFR] less than about 60 L/min and a [% predicted FEV1] less than about 50 percent" (Remarks, p.9-10).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant urges that the rejection is primarily deficient because the copending '565 claims alone do not teach or suggest the instantly claimed method in its entirety, but this urging is unavailing. In the instant case, the grounds for rejection clearly acknowledge that the '565 claims do not alone explicitly and identically teach the method instantly claimed. This was the purpose of citing to the secondary references to Gerhart et al. and Mahler et al., and further to the evidentiary reference to Quinn et al. Applicant's piecemeal analysis of the references cannot establish that the instant claims do not constitute an obvious variation of the '565 copending claims because it fails to consider the totality of the teachings and what they would have reasonably suggested to the ordinarily skilled artisan when taken collectively. Again, the test for obviousness is what the combined teachings would have suggested to the ordinarily skilled artisan, not each reference in a vacuum. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant's proffered position that the grounds for rejection fail to teach selecting COPD subjects for treatment with the specific PIFR and % predicted FEV1 characteristics instantly claimed is untenable. As discussed in the grounds for rejection, Mahler et al. provides teachings relevant to administering the nebulized aqueous solution of revefenacin of the '565 claims for the treatment of COPD in a COPD

subject with PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler et al. demonstrated that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 ± 5.0 L/min) and % predicted FEV1 of < about 50% (35 ± 11%) exhibited greater benefit from nebulized bronchodilator therapy as compared to dry powder inhaler therapy. To the extent that Applicant takes the position that Mahler et al. fails to teach the "selecting" of the patients based upon these PIFR and % predicted FEV1 characteristics, this position remains unavailing for the reasons addressed above in reply to the rejection under AIA 35 U.S.C. §103 (which are herein incorporated by reference).

For these reasons *supra*, rejection of claims 27-32 and 36-39 is proper.

5. Claims 27-30 and 39 are rejected on the grounds of nonstatutory double patenting as being unpatentable over claim 6 of U.S. Patent No. 8,912,334 B2 in view of Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS), each already of record, for the reasons of record set forth at p.32-34 of the previous Office Action dated July 8, 2021, of which said reasons are herein incorporated by reference.

Applicant's cancellation of claims 1-8 and 14-21 necessitates the removal of such claims from the statement of the rejection above.

Newly amended claim 27 now clarifies that the patient in step (a) of the recited method has COPD and is selected for treatment based upon a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%. As the reasons for rejection are directed to the selection of COPD subjects with PIFR of < 60 L/min and % predicted FEV1 of < 50%, such teachings as set forth in the rejection continue to meet Applicant's claims as amended.

Response to Applicant's Arguments

In reply, Applicant traverses the rejection, stating that the '334 patent claims "do[es] not teach or suggest selecting COPD patients for treatment having a [PIFR] less than about 60 L/min and a [%

predicted FEV1] less than about 50%" as presently claimed and "neither do Mahler or Quinn" (Remarks, p.10).

The arguments have been fully and carefully considered, but are not found persuasive.

As an initial matter, it should be noted that the instant rejection is set forth over the '334 claims in view of Mahler et al. – the teachings to Quinn et al. are not relied upon in the instant rejection. Accordingly, whatever deficiencies Applicant contends are present in Quinn et al. as they relate the rejection of the instant claims over those of the '334 patent are immaterial because Quinn et al. is not applied as part of the grounds for rejection (as evidence or otherwise).

Applicant urges that the rejection is primarily deficient because the '334 patent claims alone do not teach or suggest the instantly claimed method in its entirety, but this urging is unavailing. In the instant case, the grounds for rejection clearly acknowledge that the '334 claims do not alone explicitly and identically teach the method instantly claimed. This was the purpose of citing to the secondary reference to Mahler et al. Applicant's piecemeal analysis of the references cannot establish that the instant claims do not constitute an obvious variation of the '334 claims because it fails to consider the totality of the teachings and what they would have reasonably suggested to the ordinarily skilled artisan when taken collectively. Again, the test for obviousness is what the combined teachings of the references would have suggested to the ordinarily skilled artisan, not each reference as if in a vacuum. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant's proffered position that the grounds for rejection fail to teach selecting COPD subjects for treatment with the specific PIFR and % predicted FEV1 characteristics instantly claimed is untenable. As discussed in the grounds for rejection, Mahler provides teachings relevant to administering the revefenacin of the '334 claims via nebulizer for the treatment of COPD in a COPD subject with PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler demonstrated that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 $\pm$ 5.0 L/min) and % predicted FEV1 of < about 50% (35 $\pm$ 11 %) exhibited greater benefit from nebulized bronchodilator therapy as compared to dry powder inhaler therapy. To the extent that Applicant takes the position that Mahler fails to teach "selecting" patients based upon these PIFR and % predicted FEV1 characteristics, this position remains

unavailing for the reasons addressed above in reply to the rejection under AIA 35 U.S.C. §103 (which are herein incorporated by reference, but not repeated in the interest of brevity).

For these reasons *supra*, rejection of claims 27-30 and 39 is proper.

6. Claims 27-30 are rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 5 and 16 of U.S. Patent No. 10,106,503 B2 in view of Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS), each already of record, for the reasons of record set forth at p.34-37 of the previous Office Action dated July 8, 2021, of which said reasons are herein incorporated by reference.

Applicant's cancellation of claims 1-8 and 14-21 necessitates the removal of such claims from the statement of the rejection above.

Newly amended claim 27 now clarifies that the patient in step (a) of the recited method has COPD and is selected for treatment based upon a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%. As the reasons for rejection are directed to the selection of COPD subjects with PIFR of < 60 L/min and % predicted FEV1 of < 50%, such teachings as set forth in the rejection continue to meet Applicant's claims as amended.

Response to Applicant's Arguments

In reply, Applicant traverses the rejection, stating that the '503 patent claims "do[es] not teach or suggest selecting COPD patients for treatment having a [PIFR] less than about 60 L/min and a [% predicted FEV1] less than about 50%" as presently claimed and "neither does Mahler" (Remarks, p.10).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant urges that the rejection is primarily deficient because the '503 patent claims alone do not teach or suggest the instantly claimed method in its entirety, but this urging is unavailing. In the instant case, the grounds for rejection clearly acknowledge that the '503 claims do not alone explicitly and

identically teach the method instantly claimed. This was the purpose of citing to the secondary reference to Mahler et al. Applicant's piecemeal analysis of the references cannot establish that the instant claims do not constitute an obvious variation of the '503 claims because it fails to consider the totality of the teachings and what they would have reasonably suggested to the ordinarily skilled artisan when taken collectively. Again, the test for obviousness is what the combined teachings of the references would have suggested to the ordinarily skilled artisan, not each reference as if in a vacuum. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant's proffered position that the grounds for rejection fail to teach selecting COPD subjects for treatment with the specific PIFR and % predicted FEV1 characteristics instantly claimed is untenable. As discussed in the grounds for rejection, Mahler et al. provides teachings relevant to administering the nebulized revefenacin of the '503 claims for the treatment of COPD in a COPD subject with PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler et al. demonstrated that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 $\pm$ 5.0 L/min) and % predicted FEV1 of < about 50% (35 $\pm$ 11 %) exhibited greater benefit from nebulized bronchodilator therapy as compared to dry powder inhaler therapy. To the extent that Applicant takes the position that Mahler et al. fails to teach the "selecting" of the patients based upon these PIFR and % predicted FEV1 characteristics, this position remains unavailing for the reasons addressed above in reply to the rejection under AIA 35 U.S.C. §103 (which are herein incorporated by reference, but not repeated in the interest of brevity).

For these reasons *supra*, rejection of claims 27-30 is proper.

7. Claims 27-30 are rejected on the grounds of nonstatutory double patenting as being unpatentable over claims 3 and 14 of U.S. Patent No. 10,334,995 B2 in view of Gerhart et al. (U.S. Patent Application Publication No. 2016/0166506 A1; 2016) and Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, cited by Applicant on the 11/25/19 IDS),

citing to Quinn et al. ("Pharmacodynamics, Pharmacokinetics and Safety of Revefenacin (TD-4208), a Long-Acting Muscarinic Antagonist, In Patients with Chronic Obstructive Pulmonary Disease (COPD): Results of Two Randomized, Double-Blind, Phase 2 Studies", *Pulmonary Pharmacology & Therapeutics*, 2018; 48:71-79; Published Online October 4, 2017, cited by Applicant on the 11/25/19 IDS) as evidence,

each already of record, for the reasons of record set forth at p.37-40 of the previous Office Action dated July 8, 2021, of which said reasons are herein incorporated by reference.

Applicant's cancellation of claims 1-8 and 14-21 necessitates the removal of such claims from the statement of the rejection above.

Newly amended claim 27 now clarifies that the patient in step (a) of the recited method has COPD and is selected for treatment based upon a PIFR of < about 60 L/min and % predicted FEV1 of < about 50%. As the reasons for rejection are directed to the selection of COPD subjects with PIFR of < 60 L/min and % predicted FEV1 of < 50%, such teachings as set forth in the rejection continue to meet Applicant's claims as amended.

Response to Applicant's Arguments

In reply, Applicant traverses the rejection, stating that the '995 patent claims "do[es] not teach or suggest selecting COPD patients for treatment having a [PIFR] less than about 60 L/min and a [% predicted FEV1] less than about 50%" as presently claimed and "neither do Gerhart, Mahler or Quinn" (Remarks, p.11-12).

The arguments have been fully and carefully considered, but are not found persuasive.

Applicant urges that the rejection is primarily deficient because the '995 patent claims alone do not teach or suggest the instantly claimed method in its entirety, but this urging is unavailing. In the instant case, the grounds for rejection clearly acknowledge that the '995 claims do not alone explicitly and identically teach the method instantly claimed. This was the purpose of citing to the secondary references to Gerhart et al. and Mahler et al., further citing to the evidentiary reference to Quinn et al. Applicant's piecemeal analysis of the references cannot establish that the instant claims do not constitute an obvious

variation of the '995 claims because it fails to consider the totality of the teachings and what they would have reasonably suggested to the ordinarily skilled artisan when taken collectively. Again, the test for obviousness is what the combined teachings of the references would have suggested to the ordinarily skilled artisan, not each as if in a vacuum. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant's proffered position that the grounds for rejection fail to teach selecting COPD subjects for treatment with the specific PIFR and % predicted FEV1 characteristics instantly claimed is untenable. As discussed in the grounds for rejection, Mahler et al. provides teachings relevant to administering the nebulized revefenacin of the '995 claims for the treatment of COPD in a COPD subject with PIFR of < about 60 L/min and % predicted FEV1 of < about 50% because Mahler et al. demonstrated that COPD patients with suboptimal PIFR of < 60 L/min against the DISKUS DPI (53.3 $\pm$ 5.0 L/min) and % predicted FEV1 of < about 50% (35 $\pm$ 11 %) exhibited greater benefit from nebulized bronchodilator therapy as compared to dry powder inhaler therapy. To the extent that Applicant takes the position that Mahler et al. fails to teach the "selecting" of the patients based upon these PIFR and % predicted FEV1 characteristics, this position remains unavailing for the reasons addressed above in reply to the rejection under AIA 35 U.S.C. §103 (which are herein incorporated by reference, but not repeated in the interest of brevity).

For these reasons *supra*, rejection of claims 27-30 is proper.

Conclusion

Rejection of claims 27-39 is proper.
No claims of the present application are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (M.P.E.P. §§ 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line (or paragraph) numbers (if available) in the as-filed specification, not the published application. Due to the procedure outlined in M.P.E.P. § 2163.06 for interpreting claims, other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is reminded that MPEP §2001.06(b) clearly states that "[t]he individuals covered by 37 C.F.R. 1.56 have a duty to bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United

States applications which are "material to patentability" of the application in question." See *Armour & Co. v. Swift & Co.*, 466 F.2d 767, 779, 175 USPQ 70, 79 (7th Cir. 1972). MPEP §2001.06(b) clearly indicates that "if a particular inventor has different applications pending in which similar subject matter but patentably indistinct claims are present that fact must be disclosed to the examiner of each of the involved applications." See *Dayco Prod. Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1365-69, 66 USPQ2d 1801, 1806-08 (Fed. Cir. 2003).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached Monday through Friday (08:30 AM to 05:00 PM).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

December 23, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

183577 7590 09/14/2022

Sheppard Mullin Richter & Hampton LLP/Theravance
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

EXAMINER
DRAPER, LESLIE A ROYDS

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 09/14/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/555,216	08/29/2019	CHRISTOPHER NOEL BARNES	P-340-US1/71TD-343864-US	8316

TITLE OF INVENTION: METHODS FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	12/14/2022

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

183577 7590 09/14/2022
Sheppard Mullin Richter & Hampton LLP/Theravance
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/555,216	08/29/2019	CHRISTOPHER NOEL BARNES	P-340-US1/71TD-343864-US	8316

TITLE OF INVENTION: METHODS FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1200	$0.00	$0.00	$1200	12/14/2022

EXAMINER	ART UNIT	CLASS-SUBCLASS
DRAPER, LESLIE A ROYDS	1629	514-332000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/555,216	08/29/2019	CHRISTOPHER NOEL BARNES	P-340-US1/71TD-343864-US	8316

183577 7590 09/14/2022

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EXAMINER	
DRAPER, LESLIE A ROYDS	
ART UNIT	PAPER NUMBER
1629	

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Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/555,216	Applicant(s) BARNES et al.	
	Examiner Leslie A Royds Draper	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the request for continued examination filed 29 March 2022.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 27-35 and 39 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 29Mar22.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☑ Other No drawings filed.

/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

A request for continued examination under 37 C.F.R. §1.114, including the fee set forth in 37 C.F.R. §1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. §1.114, and the fee set forth in 37 C.F.R. §1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. §1.114. Applicant's submission filed on March 29, 2022 has been entered.

Applicant's Information Disclosure Statement filed March 29, 2022 (one page total) has been received and entered into the present application. As reflected by the attached, completed copy of form PTO/SB/08b, the Examiner has considered the cited references.

Claims 27-35 and 39 remain pending and under examination.

Claim 27 is amended.

Claims 36-38 are cancelled.

EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE

For clarity of the record, Applicant is reminded that instant claims 27-35 and 39 are entitled to the benefit of the effective filing date of the earlier-filed U.S. Provisional Patent Application No. 62/724,805, filed August 30, 2018, as previously stated at p.3 of the July 8, 2021 non-final Office Action.

Applicant amends claim 27 to now recite "[a] method for treating chronic obstructive pulmonary disease in a patient" via specifically selecting a patient having chronic obstructive pulmonary disease (COPD) and peak inspiratory flow rate (PIFR) of < about 60 L/min and percent predicted force expiratory volume in one second (% predicted FEV1) of < about 50%, and administering to this selected patient a pharmaceutical composition comprising about 175 μg revefenacin (or pharmaceutically acceptable salt thereof) in 3 mL aqueous solution once daily via nebulizer (claim 27). Dependent claims 28-30 further limit the PIFR and/or % predicted FEV1 of the selected patient, and dependent claims 31-35 further limit the composition to require additional excipients and/or properties (e.g., pH). Dependent claim 39 specifies that the administration is performed via jet nebulizer. Revefenacin was a known long-acting muscarinic

antagonist bronchodilator effective for the treatment of COPD (Specification, p.6, l.27-29; Gerhart et al., U.S. Patent Application Publication No. 2016/0166506 A1, p.1, para.[0006], p.6, para.[0047], of record).

The closest prior art of record is Mahler et al. ("Comparison of Dry Powder versus Nebulized Beta-Agonist in Patients with COPD Who Have Suboptimal Peak Inspiratory Flow Rate", *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 2014; 27(2):103-109, already of record). Mahler et al. teaches an experimental study designed to determine "whether using a threshold of PIFRresist of <60 L/min against a specific DPI [dry powder inhaler] is a useful criterion for when to use a nebulizer to deliver bronchodilator medications", as DPI delivery may not achieve clinical benefit in patients unable to inhale a dry powder bronchodilator due to low PIFR (col.1, para.1, p.103; col.1, para.3, p.108). Mahler et al. teaches the selection of 20 COPD patients with PIFR of < 60 L/min (53.3 $\pm$ 5.0 L/min) to determine if lung function measured at 2 hr post-dose would be greater with a β-agonist bronchodilator delivered by nebulization than with inhalation from a DPI (col.1, para.2-3, p.104). Although not specifically selected on the basis, the 20 COPD subjected also exhibited a % predicted FEV1 of 35 $\pm$ 11 (Table 2, p.106). Mahler et al. reported that at peak effect (2 hr post-dose), volume responses as measured by forced vital capacity (FVC) and inspiratory capacity (IC) were significantly higher with nebulized arformoterol solution, as compared to salmeterol dry powder, with no significant change in FEV1 (abstract; Table 3, p.106). Mahler et al. concludes that "[b]ronchodilator therapy via nebulization should be considered in patients with COPD who have a suboptimal PIFRresist against a particular DPI" of <60 L/min (abstract). Mahler et al. did not specifically study the effects of long-acting muscarinic antagonist (LAMA) bronchodilator therapy in this population.

Applicant's working example of the as-filed specification presents an experimental study of LAMA bronchodilator therapy administered via nebulizer or DPI to COPD subjects with PIFR of <60 L/min (Ex.1, p.13, l.13-31). Applicant teaches that the 28 days study compared the effects of once-daily LAMA revefenacin (175 μg in 3 mL of an isotonic, sterile aqueous solution containing sodium chloride, citric acid, sodium citrate, and water for injection at pH 5.0) delivered via nebulizer, as compared to once-daily LAMA tiotropium (18 μg/day) via DPI, on lung function in these COPD patients with low PIFR (<60 L/min) after the 28 day administration period (Ex.1, p.13, l.13-30). Applicant observed that "there were trends favoring

revefenacin administered using a nebulizer over tiotropium administered using a [DPI] for trough FEV1 and FVC, but such trends did not meet statistical significance nor clinical relevance" (Ex.1, p.15, l.4-7; Table 2, p.15; Tables 3-4, p.16). However, Applicant observed that "in subjects with more severe airflow limitation (FEV1 <50% predicted), there were statistically significant and clinically relevant greater improvements in both trough FEV1 and FVC for revefenacin administered using a nebulizer compared to tiotropium administered using a [DPI]", though "[n]o differences in trough IC were noted" (Ex.1, p.15, l.7-11; Table 2, p.15; Table 3-4, p.16).

Applicant's working example demonstrates that a comparison of LAMA bronchodilator therapy administered via DPI to LAMA bronchodilator therapy administered via nebulizer in COPD patients with suboptimal PIFR of <60 L/min does not provide statistically significant changes in lung function as measured by FEV1, FVC and IC, but a specific subpopulation of COPD patients with suboptimal PIFR of <60 L/min and % predicted FEV1 of <50% did show statistically significant changes in lung function as determined by measures of obstruction (FEV1 and FVC) relevant to severity of COPD. Accordingly, Applicant's working example demonstrates that following the suggestion of Mahler's publication – i.e., selecting COPD patients with suboptimal PIFR of <60 L/min for nebulized bronchodilator therapy – would not yield these therapeutically beneficial and statistically significant effects on lung function as measured by FEV1 and FVC when administered LAMA bronchodilator therapy, as shown by Applicant's working example. Rather, Applicant demonstrates that it is the specific coupling of suboptimal PIFR of <60 L/min with % predicted FEV1 of <50% that yields these therapeutically beneficial and statistically significant effects on lung function as measured by FEV1 and FVC. Note that the working example properly compares the effects of LAMA bronchodilator therapy administered via nebulizer versus LAMA bronchodilator therapy administered via DPI, thereby comparing bronchodilators of like mechanism to determine the effect of administration route (nebulizer or DPI) on lung function in these specific COPD populations.

It is reiterated that Mahler's teachings, taken as a whole, specifically suggest the use of nebulized bronchodilator therapy versus DPI in COPD subjects with suboptimal PIFR <60 L/min, and makes no specific suggestions about particularly selecting COPD subjects for nebulized bronchodilator therapy that

exhibit both suboptimal PIFR of <60 L/min *and* % predicted FEV1 of <50%. However, even if Mahler's teachings were interpreted as suggesting this population with PIFR <60 L/min and % predicted FEV1 of <50% (because the study subjects used therein exhibited % predicted FEV1 of 35 $\pm$ 11; Table 3, p.106), then at best the ordinarily skilled artisan would have reasonably expected that nebulized bronchodilator therapy would have yielded significant changes in FVC and IC, but not FEV1. Applicant, on the other hand, has demonstrated an unexpected difference in that the administration of nebulized LAMA revefenacin bronchodilator therapy did, in fact, yield a significant change in FEV1 in the claimed population of COPD subjects. For these reasons, Applicant's claimed method is understood to patentably distinguish over this closest prior art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Claims 27-35 and 39 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds Draper whose telephone number is (571)272-6096. The examiner can normally be reached Monday through Friday (08:30 AM to 05:00 PM).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571)-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Leslie A. Royds Draper/
Primary Examiner, Art Unit 1629

September 5, 2022